LONG-ACTING SULPHONAMIDES AND PROTEIN-BINDING

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RECENTLY there has been much interest in new sulphonamides which produce persistently high blood-levels with a single daily dose. These concentrations are comparable to those produced by the established regime of giving sulphadimidine every six hours.

Two long-acting sulphonamides of this type are sulphaphenylpyrazole ('Orisulf') and sulphamethoxypyridazine ('Lederkyn'). Experimentally it was found that they were only slowly acetylated and that they penetrated little into cerebrospinal fluid (Rentchnick 1958). Though in-vitro these compounds had similar antibacterial activity to sulphadiazine, some of the results of clinical trials were disappointing (Harris et al. 1957, Prlina et al. 1958). Better results were claimed when larger doses were used (Walker and Hambukger 1957, Grieble and Jackson 1958, Jefferson 1958). These features of lengthy action, slow acetylation, poor penetration, and possibly inferior therapeutic activity suggested the present study on the degree to which these new sulphonamides were attached to plasma-proteins, and the effect of any such binding on their persistence in the blood, antibacterial action, and penetration into tissue-fluids. The compounds studied were sulphaphenylpyrazole, sulphamethoxypyridazine, and sulphachloropyridazine. This last compound was included because of its close chemical similarity to sulphamethoxypyridazine, and because the duration of its action is brief (Jones et al. 1957). These compounds were compared with two well-established compounds—sulphadimidine and sulphadiazine.

Methods

Chemical Estimation of Sulphonamides

This was based on the method of Bratton and Marshall (1939), in which napthyl-ethylene-diamine-dihydrochloride is used as the coupling agent to produce the colour. Optical densities were measured in a 'Spekker Absorptiometer' H.760.301. These were converted to sulphonamide concentrations using calibration lines prepared by adding sulphonamide to plasma or urine. This was necessary as the recovery varied with the fluid analysed. Blank readings were deducted as some colour was often produced in urine before any sulphonamide was given. Free sulphonamide was estimated, and then total sulphonamide by hydrolysing plasma or urine with 0·01 *N* hydrochloric acid at 100°C for sixty minutes. The difference between these estimations represented the amount of acetylated sulphonamide.

Protein-binding of Sulphonamides

The degree of attachment of sulphonamides to protein was measured by dialysing human plasma to which sulphonamide had been added, against phosphate buffers. Aseptic technique was used in separating the plasma and in constructing the dialysis units, to prevent the growth of microorganisms during equilibration. Each unit was a sac of Visking dialysis tubing, containing 10 ml. of phosphate buffer within a 25 ml. screw-capped container, and the whole was sterilised by autoclaving After cooling, 10 ml. of plasma containing varying concentrations of sulphonamide was added around each sac. The units were agitated for twelve hours at 37°C, to allow equilibration of the diffusible constituents between plasma and buffer. Sulphonamide concentrations were then estimated in outer and inner fluids. The concentration of diffusible sulphonamide was given by the concentration within the sac, whereas in the outer fluid there was both diffusible and protein-bound sulphonamide. In calculating the results, allowance for space occupied by protein in plasma-water was made, as suggested by Davis (1942).

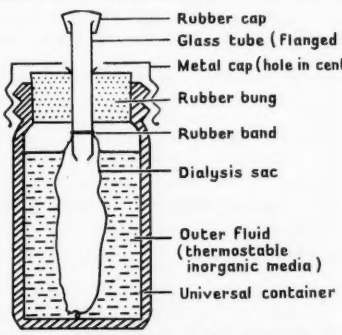

Fig. 1—Dialysis unit used for preparing sterile media to determine antibacterial activity of protein-bound sulphonamide.

Acetylation Site in the Liver

Acetylation-rate was measured by perfusing sulphonamide through isolated rabbit liver. The liver was perfused at a constant rate of 140 ml. per minute through a cannula in the portal vein, and the system was maintained at 37°C. A constant level in the upper reservoir was maintained by a Dale Schuster pump, which returned the perfused fluid from the lower reservoir. Oxygenation was effected by spraying the returning perfusate in an atmosphere of oxygen on to the walls of the upper reservoir. Samples of the perfusion fluid were withdrawn at intervals and analysed for free and total sulphonamides.

Antibacterial Action and Protein-bound Sulphonamide

This was measured by comparing the growth of a strain of *Staphylococcus aureus* in two media identical in diffusible constituents but only one of which contained protein. Minimal bacteriostatic concentrations of various sulphonamides were then measured using these two media. The media were prepared using a dialysis unit (fig. 1) which could easily be assembled and dismantled aseptically. To each unit, 10 ml. of basic inorganic salts was added on the outside of the dialysis sac. These salts were thermostable and were sterilised by heating at 115°C for thirty minutes. Further salts were necessary for growth; but, as precipitation occurred on heating, they were sterilised individually and then added to sterile human plasma (table I). 10 ml. of this fortified plasma was

TABLE I—COMPOSITION OF BACTERIOLOGICAL MEDIA BEFORE DIALYSIS

Medium	Constituent	Amount	Sterilisation
Basic inorganic	KH_2PO_4 $(NH_4)_2SO_4$ NaOH Distilled water	6·8 g. 1·0 g. To desired pH To 1000 ml.	Sterilised at 115°C for 30 min. in autoclave
Plasma	$MgSO_4$ $CaCl_2$ $FeSO_4$ $7H_2O$ Glucose Sterile human plasma	19·72 mg. in 0·5 ml. 20·0 mg. in 0·5 ml. 1·0 mg. in 0·5 ml. 5·0 g. in 10·0 ml. To 1000 ml.	Aqueous solution sterilised individually and added to plasma aseptically

injected into each sac, and the sacs were agitated at 37°C for twelve hours. Larger volumes of inner and outer fluids were obtained by pooling. Increasing concentrations of various sulphonamides were then prepared in each fluid by adding 0·5 ml. of sulphonamide solutions of different concentrations to 4·5 ml. of fluid. Each tube was inoculated with 0·18 million organisms from a diluted twenty-four-hour culture of *Staph. aureus*, and incubated at 37°C overnight. The inoculum size was critical because, if too many organisms were initially introduced, it was difficult to determine the minimum bacteriostatic concentration by a plating technique. Growth in both media was assessed by measuring changes in pH and the ability of a loopful to produce colonies on an agar plate. Clot formation was noted in the dialysed plasma, and dialysed non-proteinous fluid was examined for turbidity. Protein-binding of sulphonamide in the plasma was measured as already described. The particular strain of *Staph. aureus* chosen was inhibited by concentrations of sulphonamides which could readily be achieved in the blood-stream by therapeutic doses. Preliminary experiments showed that human plasma had no direct inhibiting action on the growth of this organism.

Results

Plasma Levels in Rabbits and Man

Concentrations of free and conjugated sulphonamide were measured in rabbits following 50 mg. of various sulphonamides given orally or intravenously (table II). Sulphadimidine was cleared within six hours and sulphamethoxypyridazine within twelve hours. Sulphaphenylpyrazole persists very long in rabbits, being still detectable after seventy-two hours. In man these relative durations are different (table III). When 1 g. of each sulphonamide was given one hour before breakfast it was found that sulphadimidine was cleared within twenty-four hours, whereas sulphamethoxypyridazine was detectable after seventy-two hours. Sulphaphenylpyrazole was of intermediate duration, being cleared within forty-eight hours. The slow rate of acetylation of these two long-acting sulphonamides was striking in comparison with the rapid acetylation of sulphadimidine. Sulphachloropyridazine disappeared from the blood as rapidly as sulphadimidine, even though it is chemically very similar to sulphamethoxypyridazine; but, unlike sulphadimidine, it was slowly acetylated.

Urine analyses from these experiments confirmed the above results on duration of the drugs in the body and the extent of acetylation.

TABLE IV—PLASMA AND CEREBROSPINAL-FLUID CONCENTRATIONS OF SULPHONAMIDE IN MAN

Compound	Dose (g.) by mouth	Time interval between dose and samples (hr.)	Concentration of free sulphonamide (mg. per 100 ml.)	
			Plasma	C.S.F.
Sulphaphenylpyrazole	1	5·0	4·6	0
	1	6·5	12·2	0
	1	7·5	6·7	0
	1	19·0	3·7	0
	1	19·5	0·5	0
	1	20·5	2·2	0
	1	22·0	0·8	0
Sulphamethoxypyridazine	1	6·0	10·0	0·7
	1	19·0	5·2	0·4
	1	20·0	4·6	0·4
	2	8·0	12·0	0·8
	2	8·0	15·5	1·3
Sulphadimidine	1	6–8	0·9	0·3
	1	6–8	3·4	0·5
	1	6–8	4·0	0·5
	1	6–8	1·5	0·6
	1	6–8	7·0	1·2
	1	6–8	7·8	1·2
	3	6–8	14·5	1·6

Concentration in Cerebrospinal Fluid

The degree of penetration of these sulphonamides into cerebrospinal fluid was measured following varying doses. The lumbar puncture, which was a diagnostic procedure in these patients, was performed between four and twenty-four hours after the dose. The protein concentration of all these lumbar fluids was normal. Sulphadimidine penetrated more readily than sulphamethoxypyridazine, as it was found in higher concentrations in the cerebrospinal fluid with similar plasma levels (table IV). Sulphaphenylpyrazole was not detected in cerebrospinal fluid even though high plasma levels were achieved and adequate time was allowed for diffusion.

TABLE II—MEAN PLASMA CONCENTRATIONS (MG. PER 100 ML. ± S.E.) OF FREE (F) AND ACETYLATED (A) SULPHONAMIDE IN RABBITS AFTER 50 MG. BY VEIN

Compound	No. of rabbits	Hours after injection															
		1		3		6		9		12		24		48		72	
		F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A
Sulphaphenylpyrazole	6	7·8 ±0·5	1·4 ±0·4	5·7 ±0·5	2·3 ±0·5	3·6 ±0·6	2·7 ±0·5	2·8 ±0·5	2·8 ±0·5	2·3 ±0·4	2·5 ±0·5	1·0 ±0·2	2·1 ±0·4	0·3 ±0·1	1·4 ±0·5	0 0	1·0 ±0·4
Sulphamethoxypyridazine	6	4·5 ±0·6	2·7 ±0·4	1·5 ±0·4	2·7 ±0·6	0·3 ±0·2	1·5 ±0·8	0·1 ±0·9	0·6 ±0·5	..	..	..	..	..	..	..	..
Sulphachloropyridazine	6	2·7 ±0·3	1·3 ±0·1	0·6 ±0·1	0·5 ..	0·1 ..	0·2 ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..
Sulphadimidine	6	1·3 ±0·6	3·6 ±0·8	0·2 ±0·2	1·5 ±0·3	0 0	0·5 ±0·2	..	..	..	..	..	..	..	..	..	..

TABLE III—MEAN PLASMA CONCENTRATIONS (MG. PER 100 ML. ± S.E.) OF FREE (F) AND ACETYLATED (A) SULPHONAMIDE IN MAN AFTER 1 G. BY MOUTH

Compound	No. of subjects	Hours after oral dose															
		1		3		6		9		12		24		48		72	
		F	A	F	A	F	A	F	A	F	A	F	A	F	A	F	A
Sulphaphenylpyrazole	9	1·8 ±0·5	0	5·9 ±0·5	0·3	6·3 ±0·5	0·3	5·6 ±0·4	0·5	4·5 ±0·4	0·4	2·1 ±0·3	0·4	0·5 ±0·8	0·3	0	0·2
Sulphamethoxypyridazine	7	4·9 ±0·9	0·1	8·5 ±0·5	0·3	9·5 ±0·6	0·5	8·8 ±0·5	0·7	8·3 ±0·5	0·9	5·8 ±0·2	1·1	3·4 ±0·3	0·8	1·8 ±0·3	0·5
Sulphachloropyridazine	2	9·2	0·5	7·5	0·6	4·6	0·6	2·9	0·6	2·0	0·6	0·3	0·2	0	0	0	0
Sulphadimidine	8	2·6 ±0·6	1·0	3·8 ±0·5	2·0	3·0 ±0·5	2·5	1·8 ±0·5	2·2	1·2 ±0·4	1·6	0·2	0·6	0	0·1	0	0

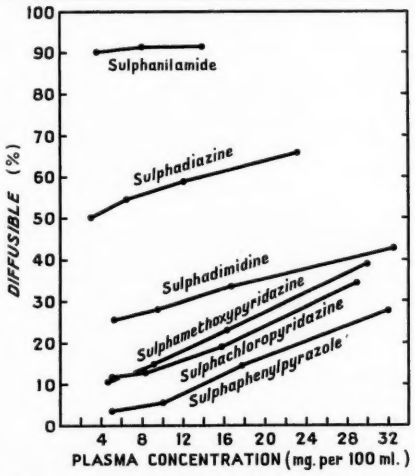

Fig. 2—Effect of increasing concentration of various sulphonamides on binding of sulphonamide to plasma-proteins at pH 7·4.

Degree of Protein-binding

All the new sulphonamides were more extensively bound to plasma-protein than sulphadimidine. This applied to plasma from both rabbits and man (fig. 2). Sulphaphenylpyrazole was bound to the greatest extent. The degree of attachment to plasma-proteins varied with both pH and concentration of sulphonamide. There is a striking increase in binding as pH changes from acidity to alkalinity, and this increase is greater with the less extensively bound compounds (fig. 3). It is therefore most important to control the pH when performing binding experiments. Degree of protein-binding decreases with increasing concentration of sulphonamide (fig. 2).

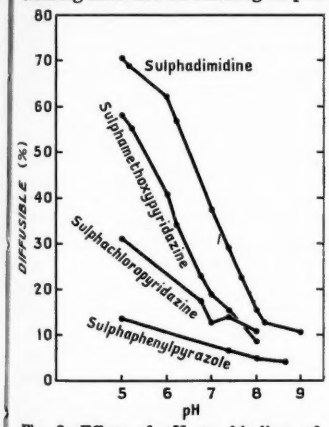

Fig. 3—Effect of pH on binding of sulphonamide to plasma-proteins at sulphonamide concentration of 10 mg. per 100 ml.

A concentration of 10 mg. sulphadimidine per 100 ml. plasma is commonly regarded as a satisfactory therapeutic level. This produces a diffusible concentration of 2·9 mg. per 100 ml., which has accordingly been used as a reference standard. The total concentration of the various sulphonamides required to produce this diffusible level is shown in table v. The new sulphonamides had to be present in higher total concentration. In the case of sulphaphenylpyrazole the total plasma concentration necessary was nearly twice that of sulphadimidine.

Acetylation and Protein-binding

Acetylation of each sulphonamide was measured by perfusing rabbit liver with the drug dissolved in dialysed non-proteinous fluid obtained as in the protein-binding experiments. The rate of acetylation was measured until the rate slowed. Dialysed plasma containing the same concentration of sulphonamide was then perfused, and the rates of acetylation were compared. The initial rate varied with each liver, but after plasma perfusion a final perfusion without plasma was done, and the initial rate was always regained (figs. 4 and 5). Plasma had no effect on the acetylation-rate of sulphadimidine but produced a reduction with sulphamethoxypyridazine and sulphachloropyridazine. The most striking slowing of acetylation-rate in the presence of plasma was found with sulphaphenylpyrazole. This order of effect agrees with the degree of protein-binding of these compounds.

Antibacterial Activity of Protein-bound Sulphonamide

An example of an antibacterial experiment is shown in fig. 6. The concentration of sulphamethoxypyridazine in dialysed non-proteinous fluid required to inhibit growth is within the range 5×10^{-5} mol. and 10×10^{-5} mol., whereas in dialysed plasma it is between 35 and 40 $\times$ 10^{-5} mol. However, the latter range in plasma gave diffusible concentrations which were similar to the minimal bacteriostatic concentration of the dialysed non-proteinous fluid. The higher concentration of sulphonamide required with each particular compound in the presence of plasma always equalled the amount that was bound to protein. The results with the other compounds are shown in table VI, where there is evident agreement between minimum bacteriostatic concentration without plasma and the concentration of diffusible sulphonamide when plasma was present. It should be emphasised that minimal bacteriostatic concentrations for the various compounds cannot be directly compared. The experiments with each sulphonamide were done on separate days and no attempt was made to compare the relative antibacterial activity of these sulphonamides in the absence of protein.

TABLE V—PLASMA CONCENTRATIONS OF SULPHONAMIDES REQUIRED TO PRODUCE THE SAME DIFFUSIBLE CONCENTRATION

Sulphonamide	Plasma concentration (mg. per 100 ml.) necessary to produce a diffusible concentration of 2·9 mg. per 100 ml.
Sulphaphenylpyrazole ..	18·6
Sulphamethoxypyridazine ..	14·0
Sulphachloropyridazine ..	15·5
Sulphadimidine	10·0
Sulphadiazine	5·5

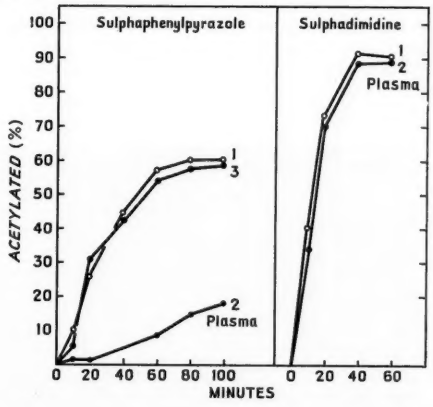

Fig. 4—Effect of plasma on rate of acetylation of sulphaphenylpyrazole and sulphadimidine.

Rabbit liver perfused in order with sulphonamide contained in non-proteinous fluid (1), plasma (2), and non-proteinous fluid (3).

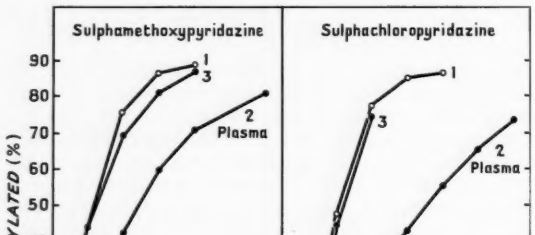

Fig. 5—Effect of plasma on rate of acetylation of sulphamethoxypyridazine and sulphachloropyridazine.

Rabbit liver perfused in order with sulphonamide contained in non-proteinous fluid (1), plasma (2), and non-proteinous fluid (3).

Antibacterial Activity of Sulphaphenylpyrazole in Man

8 patients with urinary-tract infections were studied. 5 had acute cystitis or pyelonephritis, and 3 had chronic urinary infection. In each case the causal organism was sensitive initially to less than 100 μg. of sulphonamide on a paper disc. The patients were given 2 g. of sulphaphenylpyrazole on the first day and then 1 g. daily for ten days. This produced plasma concentrations between 5 and 10 mg. per 100 ml. for most of the time and at least 50 mg. per 100 ml. of free sulphonamide in urine. This therapy did not produce disappearance of organisms or leucocytes from the urine in any patient. 2 of the patients with acute infection had some temporary improvement in symptoms. After the treatment 4 patients were successfully treated with sulphadimidine. Organisms from 2 of the remaining 4 cases had become resistant to sulphonamide, and all 4 were successfully treated with antibiotics.

Discussion

Previous attempts have been made to measure the degree of attachment of sulphonamide to plasma-protein (Davis 1942). Much less information is available concerning the antibacterial activity of sulphonamide bound to human plasma. Anton (1959) found that sulphonamide bound to bovine albumin had no antibacterial activity. It is clear from the present results that some of the new sulphonamides are bound to plasma-protein to a much greater extent than sulphadimidine or sulphadiazine, and that bound sulphonamide is not active against bacterial growth. Bacteria usually multiply in tissue planes, and the tissue-fluid concentration of sulphonamide will be similar to the diffusible plasma concentration. Thus, with extensive protein-binding, small tissue-fluid concentrations would be expected and the small amounts of sulphamethoxypyridazine and sulphaphenylpyrazole found in cerebrospinal fluid are a reflection of this (Boger 1959). The poor penetration of sulphaphenylpyrazole into cerebrospinal fluid was observed by Rentchnick (1958), but he found high concentrations in patients with meningitis. These might, however, be due to the passage of inactive protein-bound sulphonamide, as the protein concentration of the fluid increases in meningitis.

It is the usual practice to compare in-vitro antibacterial activities of sulphonamides in media containing either low concentrations of protein or no protein at all. Comparisons in such media have shown that the new sulphonamides have similar antibacterial activities to sulphadiazine (Harris et al. 1958, Niepp et al. 1958). The generally recommended doses of the new sulphonamides were chosen to give total plasma concentrations similar to those considered adequate for therapy with sulphadiazine and sulphadimidine. Much lower tissue concentrations will result, and antibacterial activity will thus be less. This may account for the poor results in urinary infections with 1 g. daily doses of sulphaphenylpyrazole and for the results of Harris et al. (1957) and Prlina et al. (1958) with 0·5 g. daily doses of sulphamethoxypyridazine.

TABLE VI—RELATIONSHIP BETWEEN DIFFUSIBLE SULPHONAMIDE CONCENTRATION, MINIMUM BACTERIOSTATIC CONCENTRATION IN PLASMA, AND MINIMUM BACTERIOSTATIC CONCENTRATION IN NON-PROTEINOUS FLUID (pH 7·0)

Sulphonamide	Diffusible sulphonamide concentration as percentage of minimum bacteriostatic concentration in plasma	Minimum bacteriostatic concentration of sulphonamide in non-proteinous fluid as percentage of the minimum bacteriostatic concentration in plasma
Sulphaphenyl-pyrazole	10–12	10–16
Sulphamethoxy-pyridazine	18·5–20·5	14·3–25
Sulphachloro-pyridazine	11·3–15·0	9·0–16·6
Sulphadimidine	39·2–39·6	36·3–41·6

The rate of acetylation of sulphonamides is also obviously related to the degree of protein-binding. These new sulphonamides are acetylated at much lower rates than sulphadimidine; and this is a useful feature, as acetylated sulphonamide has no antibacterial activity but retains toxic properties. Unfortunately the slow acetylation-rates are produced by the same mechanism which reduces the tissue-fluid concentration.

The mechanism of the delayed excretion and hence maintained plasma concentrations of the sulphaphenylpyrazole and sulphamethoxypyridazine is not yet defined. Clearly it is not directly related to protein-binding since sulphachloropyridazine is quickly excreted and yet

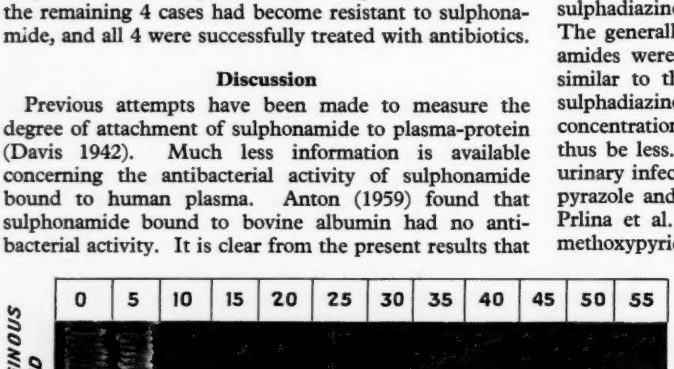

Fig. 6—Determination of minimum bacteriostatic concentration of sulphamethoxypyridazine by plating technique, showing effect of sulphamethoxypyridazine in plasma and non-proteinous fluid on growth of *Staph. aureus* at pH 7 (concentrations given in mol.×10^{-5}).

bound to protein to a greater extent than sulphamethoxypyridazine. Differential renal handling probably accounts for their slow excretion. There is also a striking species difference in excretion as the excretion-rates for sulphaphenylpyrazole and sulphamethoxypyridazine were reversed in rabbits and man. Thus this animal is unsuitable for screening new sulphonamides, particularly with respect to prolonged plasma levels.

Our results suggest that the therapeutic value of these new sulphonamides does not surpass that of the older compounds. It seems likely that for successful therapy with these highly protein-bound sulphonamides greater plasma concentrations will be required than are necessary with sulphadimidine or sulphadiazine. Toxic effects with these newer drugs have already been described (Holsinger et al. 1958, Lindsay et al. 1958, Schwartz and Norton 1958), and if larger doses have to be employed for therapeutic activity the patient may be exposed to a greater risk than that associated with sulphadimidine.

Summary

New long-acting sulphonamides, such as sulphaphenylpyrazole and sulphamethoxypyridazine, are more extensively bound to plasma-protein than the older sulphonamides, such as sulphadimidine and sulphadiazine.

Extensive protein-binding leads to lower plasma diffusible concentrations and therefore lower concentration in compartments such as cerebrospinal fluid.

Antibacterial activity depends on diffusible concentration of sulphonamide. Protein-bound sulphonamide has no antibacterial activity. Acetylation-rates also depend on diffusible concentration, and thus highly protein-bound sulphonamides are only slowly acetylated.

Rate of renal excretion does not depend solely on protein-binding since sulphachloropyridazine, which is highly protein-bound, is nevertheless rapidly eliminated in the urine.

Higher total plasma concentrations are required with the newer sulphonamides than with the older ones, to produce similar diffusible concentrations and similar therapeutic effect. These higher plasma concentrations may increase the liability to toxic effects.

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LATE EFFECTS OF LUMBAR SYMPATHECTOMY
ON BLOOD-FLOW IN THE FOOT IN OBLITERATIVE VASCULAR DISEASE

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WHILE the effect of sympathectomy on blood-flow has often been investigated in non-occlusive vascular disease, especially in the upper limb, there have been no extensive investigations of its long-term effects in patients with obliterative vascular disease of the lower limb. Of particular importance is the effect on blood-flow in the foot, since the prime indication for sympathectomy today is an ischæmic foot in a limb not suitable for some form of direct arterial surgery. In this paper I present the results of blood-flow measurements in all the available surviving, non-amputated, members of a consecutive series of 100 patients sympathectomised between one and seven years previously for obliterative vascular disease. As rather more than half the patients were operated on by me, and the remainder by one other surgeon, the technique of operation was fairly uniform.

The findings of the clinical review are fully dealt with elsewhere (Gillespie 1960a). 25 patients were dead, 8 survivors had had a major amputation, and 2 patients were untraced. Of the remaining 65, 61 were fit enough and

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TABLE I—COMPARISON OF RESTING BLOOD-FLOWS IN DENERVATED AND NON-DENERVATED FEET OF 46 PATIENTS WITH UNILATERAL SYMPATHECTOMY FOR OBLITERATIVE DISEASE

Patient	Interval between operation and test (years)	Foot blood-flow (ml. per 100 ml. per min.)		Comment
		Symp. limb (s.)	Non-symp. limb (N.S.)	
18	5	3·0	1·8	S. 1·7 times N.S.
19	5	2·3	1·9	1·2
23	5	3·2	1·9	1·7
30	4	2·9	1·7	1·7
33	4	2·5	1·7	1·5
38	4	2·8	2·0	1·4
40	3½	3·0	1·5	2·0
41	4	6·7	1·0	6·7
43	3½	3·5	1·2	2·9
44	3½	4·2	2·4	1·8
50	3½	4·1	1·3	3·2
61	3	9·7	2·6	3·7
64	2½	1·7	1·1	1·5
66	2½	5·5	1·6	3·4
70	2½	5·4	1·4	3·9
76	2	2·9	1·1	2·6
77	2	1·8	1·4	1·3
78	2	4·8	2·8	1·7
79	2	5·2	4·7	1·1
80	2	4·4	3·1	1·4
81	2	2·3	1·3	1·8
82	2	5·3	2·2	2·4
84	1½	4·3	2·8	1·5
85	2	5·6	5·0	1·1
87	1½	6·2	1·6	3·9
89	1½	3·7	2·6	1·4
90	1½	2·0	1·6	1·3
93	1½	3·0	1·3	2·3
94	1½	1·3	0·8	1·6
102	1	5·0	2·1	2·4
103	1	4·8	2·5	1·9
104	1	3·1	2·0	1·6
111	1½	4·2	4·1	1·0
114	1½	3·7	1·9	2·0
115	1½	6·2	1·5	4·1
117	1¼	2·7	1·5	1·8
120	1	4·1	3·1	1·3
121	1	2·7	1·9	1·4
63	2½	1·8	2·3	N.S. 1·3 times S.
65	3	3·6	4·0	1·1
69	2½	2·7	3·2	1·2
71	2	1·5	1·6	1·1
99	1½	1·2	4·2	3·5
101	1	1·2	1·3	1·1
108	1	2·5	2·7	1·1
113	1½	3·5	4·3	1·2

TABLE II—COMPARISON OF RESTING FOOT BLOOD-FLOWS IN THE NON-OCCLUDED AND OCCLUDED LIMBS OF 15 PATIENTS WITH UNILATERAL COMPLETE OCCLUSION OF MAIN ARTERY

Patient	Foot flows (ml. per 100 ml. per min.)	
	Occluded limb	Non-occluded limb
12	2·9	3·4
16	0·7	1·8
24	1·0	1·3
32	1·0	3·8
33	0·9	1·2
36	1·2	1·5
37	1·7	2·8
43	2·1	3·0
58	1·7	2·0
70	1·1	2·4
71	1·5	1·6
84	1·9	2·0
95	1·4	1·4
124	1·9	6·6
150	2·2	3·7
Mean flow	1·5	2·5

willing to attend for blood-flow investigations. The measurements made can thus fairly be said to reflect the average long-term effect of sympathectomy on foot blood-flow in patients with obliterative vascular disease.

For comparison, blood-flows were also measured in 18 of a consecutive series of 20 patients sympathectomised for non-obliterative disease between one and seven years previously.

Methods

Blood-flows were measured by venous occlusion plethysmography (Barcroft and Swan 1953) in a thermostatically controlled laboratory at 22°C, using water-filled plethysmographs kept at a constant temperature of 32–34°C. The collecting cuff pressures used were those yielding the maximum inflow curves: owing to the arterial occlusions they were necessarily lower than the pressures normally used. The basic resting blood-flow in the feet was recorded at half-minute intervals over a ten-minute period, after the patient had been allowed to settle for twenty minutes following fitting of the plethysmographs. Thereafter, vigorous body heating (Pickering and Hess 1933) was applied by a heat cage over the chest and head for at least twenty minutes, prolonged if necessary till the patient was sweating freely and his oral temperature had risen at least 0·3°F, and usually much more. Flows were then again recorded over a ten-minute period.

Blood-flows were calculated in millilitres per 100 ml. of foot per minute. The mean post-heating flow was expressed as a percentage increase or decrease of the mean pre-heating or resting flow (Barcroft and Hamilton 1948a and b). This change constituted the " vasomotor test".

In all, the vasomotor test was carried out in 75 limbs sympathectomised for obliterative arterial disease, and in 26 sympathectomised for non-obliterative disease. Flows were also measured in the non-sympathectomised limbs of those patients with a unilateral sympathectomy.

TABLE III—COMPARISON OF RESTING BLOOD-FLOWS IN DENERVATED AND NON-DENERVATED FEET OF 10 PATIENTS WITH UNILATERAL SYMPATHECTOMY FOR NON-OBLITERATIVE DISEASE

Patient	Interval between operation and test (years)	Foot blood-flow (ml. per 100 ml. per min.)		Comment
		Symp. limb (S.)	Non-symp. limb (N.S.)	
11	5 1/2	4·3	1·1	S. 3·9 times N.S.
29	4 1/2	8·4	2·2	3·8
42	3 1/2	5·1	0·9	5·7
56	3	3·6	2·5	1·4
75	2	10·2	3·3	3·1
95	1 1/2	5·3	1·3	4·1
96	1 1/2	4·1	1·9	2·2
98	1 1/4	4·5	1·7	2·6
106	1	8·0	3·0	2·7
15	6	2·5	4·6	N.S. 1·8 times S.

Results and Discussion

Duration of Effect of Lumbar Sympathectomy

In considering the duration of effect of lumbar sympathectomy on blood-flow one must clearly distinguish between the early falling off in the maximal flows recorded a few hours after operation (Lynn and Barcroft 1950) and the long-term effect on blood-flow. This investigation is concerned only with the latter.

46 of the patients available for blood flow-measurements had had a unilateral sympathectomy for obliterative disease. It was thus possible to compare the resting blood-flows in the sympathectomised and non-sympathectomised feet of these patients between one and seven years after operation (table I). In 38 (83%) of the 46 patients the resting blood-flow in the sympathectomised foot exceeded that in the non-sympathectomised foot, the average flow being nearly twice as great. That is, double the amount of blood was still flowing through these feet sympathectomised for obliterative vascular disease between one and seven years previously.

This figure probably underestimates the effect of sympathectomy on blood-flow in the foot, for two reasons. Firstly, if flows had been measured under normal cool environmental conditions, instead of in a warm laboratory, then vasoconstriction in the normal foot would have made the difference in flows even greater. Secondly, the resting foot blood-flow in untreated limbs with occluded arteries is often less than in more normal limbs. This is illustrated by table II, which sets out the results of blood-flow measurements in the feet of 15 untreated patients in whom aortography had demonstrated a complete arterial occlusion in one limb, the other limb being relatively free from atherosclerosis. In every patient, except 1 in whom flows in the two feet were equal, blood-flow in the foot of the occluded limb was less than in its more normal fellow. The mean foot flow in the 15 least affected limbs was 1·7 times greater than that in the occluded limbs. It therefore follows that a postsympathectomy increase of blood-flow in the occluded limbs to twice as much as that in the more normal limbs probably means that the preoperative flow has been trebled or quadrupled.

TABLE IV—EFFECT OF TIME ON THE RESTING BLOOD-FLOW IN FEET OF 46 PATIENTS WITH UNILATERAL SYMPATHECTOMY FOR OBLITERATIVE DISEASE

Interval between operation and testing (years)	Type of limb	No. of limbs	Foot blood-flow (ml. per 100 ml. per min.)	
			Mean	Range
1–7	Sympathectomised	46	3·6	1·2–9·7
	Non-sympathectomised	46	2·2	0·8–5·0
1–2	Sympathectomised	19	3·4	1·2–6·2
	Non-sympathectomised	19	2·3	0·8–4·3
2–7	Sympathectomised	27	3·8	1·5–9·7
	Non-sympathectomised	27	2·1	1·0–5·0

For comparison with the results in obliterative disease, blood-flows were also measured in 10 patients who had had a unilateral sympathectomy for non-obliterative disease between one and seven years previously (table III). In 9 the flow in the sympathectomised foot exceeded that in the non-sympathectomised foot by a mean of 3·3 times. The difference between the mean of 2·0 in the obliterative-disease group and this of 3·3 is undoubtedly in part a result of the obliterative disease process in the former, but may also partly be explained by the fact that in non-obliterative disease the resting flows in the two feet before operation are equal.

To determine whether with the passage of time the effect of a sympathectomy becomes less, it is of interest to compare the interval between operation and measurement of blood-flows with the mean difference between the flows in the sympathectomised and non-sympathectomised feet. This has been done for the 46 patients of the obliterative disease group considered as a whole, irrespective of whether flows were larger or smaller in the sympathectomised foot at the time of testing (table IV). The mean flow in all the sympathectomised feet was 3·6 ml. per 100 ml. foot per minute, compared with 2·2 ml. in the non-sympathectomised feet, the difference in flows being significant (at the 0·1% level). In those patients in whom the interval between operation and testing was between one and two years, the mean flow in the sympathectomised feet was 3·4 ml. compared with 2·3 ml. in the non-sympathectomised feet. Where the interval was two or more years, the similar figures for mean flow were 3·8 and 2·1 ml. respectively. The difference between the means at the two intervals is not significant statistically. There is thus no evidence that the effect of sympathectomy on blood-flow in the foot diminishes with the passage of time, at least between one and seven years after operation.

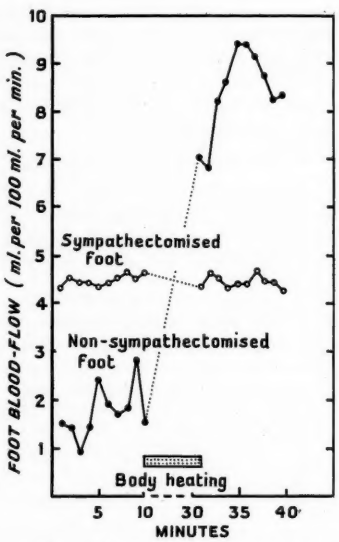

Fig. 1—A negative vasomotor test.
The patient had had a unilateral sympathectomy for non-obliterative disease 15 months previously. There is no rise in flow in the sympathectomised foot after body heating, while there is a large rise in the non-sympathectomised foot.

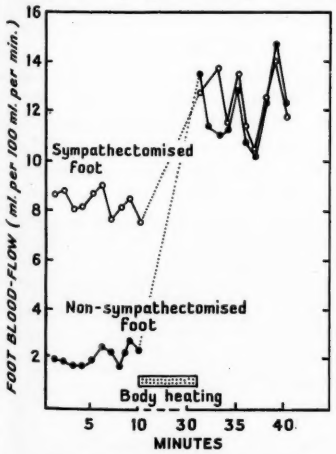

Fig. 2—A positive vasomotor test.
The patient had had a unilateral sympathectomy for non-obliterative disease 4½ years previously. There is a rise in flow in the sympathectomised foot, as well as in the non-sympathectomised foot, after body heating.

This part of the work can be summarised by stating that lumbar sympathectomy produces a lasting and important increase in blood-flow in the foot, even in obliterative vascular disease.

Evidence of Some Recovery of Vasomotor Activity

Even though a lasting doubling or trebling of blood-flow in the foot follows lumbar sympathectomy, there may be partial recovery of sympathetic vasomotor activity. The greater this recovery, the less efficacious will operation remain in preventing reflex vasoconstriction in the foot.

To determine how much recovery of sympathetic vasomotor activity did occur, the body heating test already described was employed. The principle of the test is that, if there is any recovery of sympathetic vasomotor activity, then on vigorous body heating this activity is abolished, and blood-flow in the sympathectomised foot increases. The results of a negative vasomotor test are illustrated in fig. 1. The resting flow in the sympathectomised foot is two or three times greater than in the other foot. After body heating, flow is increased fivefold in the normal foot, but remains unchanged in the sympathectomised foot. There is thus no evidence of any return of sympathetic vasomotor activity in this patient. A positive vasomotor test is illustrated in fig. 2. Here, flows in both the sympathectomised and normal feet increased with body heating, showing that there had been some recovery of vasomotor activity. This recovery is far from complete, however, since the resting flow in the sympathectomised foot was still four times greater than in the other.

These two patients had been sympathectomised, respectively fifteen months and four and a half years previously, for non-obliterative disease. Their vessels were fully capable of dilatation on body heating. Positive tests, however, are also readily obtained in obliterative disease where there has been some recovery of sympathetic vasomotor control. The results of the vasomotor test are set out in table V for the 61 patients sympathectomised for obliterative arterial disease. In making up the table only increases in blood-flow on body heating of more than 10% have been regarded as significant. Of the 75 sympathectomised limbs in these patients, 8 showed a rise in blood-flow in the foot after body heating. That is, in only 11% of these limbs was there evidence of late partial recovery of sympathetic control.

TABLE V—EFFECT OF BODY HEATING ON BLOOD-FLOW IN SYMPATHECTOMISED AND NON-SYMPATHECTOMISED FEET OF 61 PATIENTS OPERATED ON FOR OBLITERATIVE DISEASE

—	Blood-flow not increased in	Blood-flow increased in
75 sympathectomised limbs ..	67 limbs	8 limbs (11%)
46 non-sympathectomised limbs ..	10 limbs	36 limbs (78%)

It might be argued, however, that this low figure is due not to an absence of vasomotor activity but to inability of the vessels to dilate with body heating, owing to disease. It is impossible to say how far this is so, but two observations suggest that the figure is not excessively low. Firstly, although the disease process was so often bilateral, with absence of pulses in both legs, 78% of the non-sympathectomised feet of the patients with a unilateral sympathectomy for obliterative disease showed significant vasodilatation on body heating. Secondly, the figure of 11% compares well with that of 12% obtained when the body heat test was applied in 18 patients sympathectomised between one and seven years previously for non-obliterative disease (table VI). Of the 26 sympathectomised feet of these patients only 3 (12%) showed evidence of a significant return of vasomotor activity, although their vessels had a normal capacity for dilatation.

This low rate of recovery of sympathetic activity in the foot (11 or 12%) is particularly striking when compared

TABLE VI—EFFECT OF BODY HEATING ON BLOOD-FLOW IN THE SYMPATHECTOMISED AND NON-SYMPATHECTOMISED FEET OF 18 PATIENTS OPERATED ON FOR NON-OBLITERATIVE DISEASE

—	Blood-flow not increased in	Blood-flow increased in
26 sympathectomised limbs ..	23 limbs	3 limbs (12%)
10 non-sympathectomised limbs ..	0	10 limbs (100%)

with that in the hand after cervicodorsal sympathectomy. Barcroft and Hamilton (1948a and b), for example, found that in 78% of hands tested between one and six years after operation there was evidence of recovery. The incidence of vasomotor recovery in the lower limb is also much lower than that of sudomotor recovery (Gillespie 1960b).

It is of interest that even where there was some significant recovery of vasomotor activity, the increase in blood-flow on body heating seldom exceeded 50% (table VII), and the resting flow had always remained higher in these limbs than in the non-sympathectomised limbs.

It will be noted that blood-flow in the sympathectomised feet frequently became less after body heating. In the absence of any recovery of vasoconstriction tone, which would be released on body heating to give an increase in flow, this is not surprising. When generalised vasodilatation is produced by body heating, or by a vasodilator (Gillespie 1959), blood is diverted from the sympathectomised limb into the widespread new areas of reduced peripheral resistance—an example of De Bakey's hæmametakinesia, or " borrowing-lending " phenomenon (De Bakey et al. 1947).

Practical Importance of the Increased Blood-flow

As already stated, the value of lumbar sympathectomy in obliterative vascular disease is in the treatment of ischæmic skin lesions in patients in whom, for one reason or another, direct arterial surgery cannot be applied. The lasting doubling of blood-flow in the foot which occurs on

TABLE VII—PERCENTAGE INCREASE IN BLOOD-FLOW IN 11 SYMPATHECTOMISED FEET PRODUCED BY BODY HEATING IN PATIENTS WITH OBLITERATIVE AND NON-OBLITERATIVE DISEASE

Obliterative disease		Non-obliterative disease	
Patient	% increase in foot blood-flow on body heating	Patient	% increase in foot blood-flow on body heating
30	31	15	24
61	17	29	44
67	11	36	11
	57		
71	13		
82	51		
99	58		
113	11		

N.B.—Patient 67 had had a bilateral sympathectomy.

an average is likely to be important in the healing of existing skin lesions and the prevention of future ones. While 11% of limbs may show some late recovery of vasomotor activity this is always very incomplete, so that the sympathectomised foot is protected from reflex vasoconstriction. This again is presumably beneficial.

20 limbs of patients in the obliterative disease series who reported back for blood-flow measurements had been sympathectomised for an ischæmic skin lesion of the foot which had healed after operation. The mean resting blood-flow in these limbs (table VIII) was 3·7 ml. per 100 ml. foot per minute. This was well above the mean flow in the non-sympathectomised feet of the patients as a whole with obliterative disease, and was clearly a major factor in promoting healing. 4 of these limbs actually showed some significant return of vasomotor activity on the vasomotor test; but this has not detracted from the sustained good result of operation, as the feet have remained healthy.

Conclusion

Blood-flow measurements give objective physiological support for the view that lumbar sympathectomy is a good operation for promoting the healing of existing ischæmic skin lesions and the lasting prevention of further ones.

Summary

1. The late effects of lumbar sympathectomy on blood-flow in the lower limb in 61 patients suffering from obliterative vascular disease has been measured. For comparison, 18 patients sympathectomised for non-obliterative disease of the lower limbs have also been investigated.

2. Lumbar sympathectomy produced a lasting doubling or trebling of blood-flow in the foot, and there was no evidence of this falling off with time during the period of review, one to seven years after operation.

3. 11–12% of sympathectomised limbs showed partial recovery of sympathetic vasomotor activity when examined between one and seven years after operation. But this was always very incomplete.

4. The beneficial effect of operation on the healing of ischæmic skin lesions is discussed.

TABLE VIII—MEAN RESTING BLOOD-FLOW IN 20 SYMPATHECTOMISED FEET OF OBLITERATIVE-DISEASE PATIENTS OPERATED ON FOR ISCHÆMIC SKIN LESIONS, AND EFFECT OF BODY HEATING

Patient	Foot affected	Resting flow (ml. per 100 ml. per min.)	Change in flow on body heating
1	Left	3·1	32% decrease
9	Both	2·7	15
		4·8	19
58	Right	5·0	20
59	Right	3·3	18
60	Left	3·1	13
66	Left	4·8	25
69	Right	2·7	7
74	Both	6·0	20
		5·6	25
78	Right	4·8	23
93	Left	3·0	27
117	Left	2·7	7
118	Both	3·9	23
		4·9	49
94	Right	1·3	No change
69	Right	2·7	7% increase
81	Left	1·5	13
82	Left	5·3	51
113	Right	3·5	11

Patients number 58 and 82 had local amputations of the toes.

I wish to express my sincere thanks to Prof. D. M. Douglas for his interest in this work. It is also a pleasure to record my thanks to Mr. William Muir for technical assistance. Miss B. J. Kinsley kindly gave statistical advice, and Miss Margaret Mackenzie prepared the figures. The work was done in the research laboratories of the department of clinical surgery at the Royal Infirmary, Dundee, while I was in receipt of a grant from the Scottish Hospital Endowment Research Trust.

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FURTHER EXPERIENCES WITH INTRATHECAL AND SUBDURAL PHENOL
OBSERVATIONS ON TWO FORMS OF PAIN

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DURING the investigation and treatment of 164 cases of cancer, it became clear that two types of pain could be distinguished by the effects of intrathecal and subdural injections of phenol given to relieve pain. My previous articles (Maher 1955, 1957) described treatment directed against *continuous* pain, and for the relief of this pain, improved techniques are discussed below. The other type of pain is a more severe and intermittent *incident* pain, arising mainly from direct impact of bony metastases on nerve endings.

The Conduction of Pain

Before considering pain from such internal stimuli, the different nerve elements associated with pain generally will be reviewed.

A and C Fibres

The possibility of a series of nerve impulses travelling along a mixed nerve became apparent after the classical work of Erlanger and Gasser (1927), who, by studying the action-potential of nerve, found different conduction-rates in its components; and this led to a classification into alpha, beta, and gamma waves.

Later, all three waves were grouped under one title—A waves, corresponding to the large A fibres of the nerve, because it was later observed that stronger stimulation revealed other slower waves corresponding to a further set of fibres hitherto unstimulated. Those with the slowest conduction-rates (0·3–1·6 metres per sec.) were found to correspond to the small non-medullated fibres for pain and were called C fibres. The B fibres of medium speed were identified by Bishop and Heinbecker (1930) and correspond to preganglionic neurones connected with the autonomic nervous system.

At present the different nerve-fibre groups may be summarised thus:

(1) Large A fibres, size 1–20μ, conduction-rate 30–100 metres per sec. Conduct alpha, beta, and gamma waves for touch, heat and cold, pain, and motor impulses.

(2) Medium or B fibres, rate 10–20 metres per sec. Preganglionic afferents.

(3) Small C fibres, non-medullated, rate 0·3–1·6 metres per sec. Conduct impulses for pain.

Destruction of A fibres relieves pain but also removes all forms of sensation, with accompanying loss of tone and power. Destruction of small C fibres alone relieves pain, with mild cutaneous analgesia at the most—that is, cutaneous sensation remains intact with no effect on tone or movement (Maher 1957).

There are now known to be two main conducting pathways for pain at the periphery—namely, the swift A and the slow C paths.

The two pain sensations after cutaneous stimulation were first identified by Rosenbach in 1884. This observation was confirmed by Gad and Goldscheider (1892), but they were in error about the nature of the second pain, which was more correctly interpreted by Thunberg (1902).

By 1934 Gasser had shown that the first pain was conducted by A fibres and the second by C fibres. The whole question of the double pain was investigated in man by Lewis and Pochin (1937, 1938) and reviewed later by Lewis (1942). By observing that local asphyxia abolished the first pain and cocaine the second, they confirmed that two pathways were involved.

The further the point of stimulation from the cord, the greater the separation between the two pain sensations. The interval between the first and second pain was 1·9 sec. when the skin of the toe was stimulated and 0·9 sec. when the upper thigh was stimulated. The first pain, conducted by large A fibres, gave rise to reflex muscular movement.

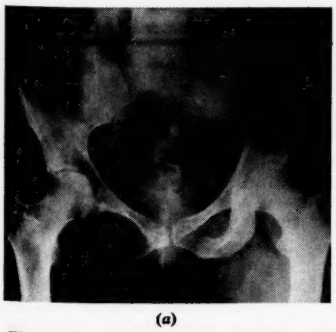
Pochin (1937, 1938) observed that the first or A pain was abolished in tabes. Here application of heat to the foot did not give rise to the first pain and immediate reflex withdrawal, but to delayed and deliberate movement later: only one pain sensation—the second—was experienced.

To summarise these findings, the first pain requires a greater stimulus to evoke it, and it is swiftly conducted, suggesting an emergency pain with accompanying defensive reflexes. The second pain is provoked by lesser stimulation, lasts longer, is slowly conducted, and could be termed a "reminder" pain at the site of injury. So far, however, these results deal largely with pain experiences produced from outside the body. It is of interest to explore how far such findings can be related to pain arising from within.

(*c*)

Recurrence of Pain after Injection of Phenol

If all *continuous* pain has ceased after injection of phenol, under what conditions can pain return in the area deprived of these afferent impulses? Firstly, regeneration by growing in of other fibres is possible, but in only 1 of my cases, after $3^1/_2$ years' total relief,



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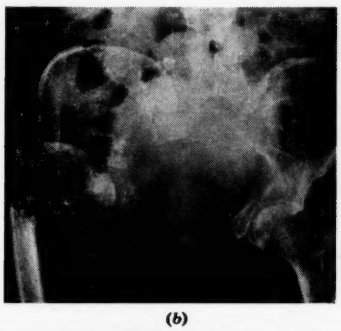

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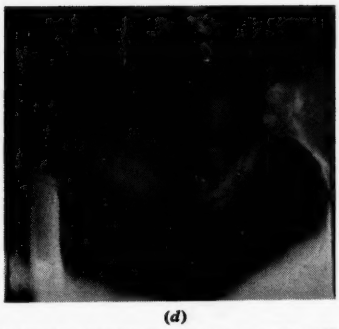

(*d*)

Fig. 1—Case 1: (*a*) invasion of right ischiopubic ramus; (*b*) pathological fracture of femur and further destruction of pelvis, June 18, 1957; (*c*) patient out of bed two days before discharge on June 30, 1957; (*d*) gross general deformity of pelvis but no pain.

has this seemed at all likely. Secondly, a further pain pathway may be stimulated. This recurrence is usually associated with fracture or vertebral collapse and these pains have been called " incident " pains.

Illustrative Cases

The following details are taken from 16 cases chosen as examples.

CASE 1.—A woman of 50, with carcinoma of the breast and metastases, underwent radical mastectomy in February, 1956, and later was given androgens and irradiation. Pain began ten months later. Fig. 1a shows invasion of the right ischiopubic ramus. From the right groin and thigh, pain areas had extended until some 18 roots were involved, illustrated on the pain segment diagram (fig. 2). Beginning on Jan. 28, 1957, intrathecal injections were given, first on the right (1 ml. of 1-in-25 phenol in glycerin, containing silver nitrate gr. $^1/_{30}$ [0·0022 g.]) at D12-L1 interspace. Injections of 1 ml. of 1-in-20 phenol were then given at L4–5 interspace on both sides and at D12–L1 on the left. She became totally free from pain.

Six weeks later she was readmitted with sudden extreme pain in the right hip. She had heard the cracking of her femur while walking in the garden. The limb was fixed between sandbags. After a few days all pain ceased spontaneously without further injections. Fig. 1b shows the fracture accompanied by further pelvic destruction, and fig. 1c shows the patient out of bed two days before discharge on June 30, 1957. Complete alleviation continued for six months until she had pain in the neck due to metastasis in the cervical spine.

On Dec. 4, 1957, subdural injection at C5–6 of 4 ml. of 1-in-10 phenol in 'Myodil' gave permanent relief for this site. The original dorsolumbar segments continued free of pain, and X-ray examination revealed further destruction of the bony pelvis, which two months later was nearly complete. Six weeks later there was gross deformity (fig. 1d) but still no pain. She died on March 22, 1958, and necropsy revealed total destruction of the bony pelvis and extensive invasion of the lower abdomen.

There were clearly two separate pain experiences. The initial pain was continuous and spread to involve most of the neurones below the groin on both sides; and it was totally relieved by successive intrathecal injections. After two months' complete relief, the severe " incident " pain of fractured femur developed suddenly within the relieved area. For this pain no further injection was required, and it subsided completely after a week or so with rest and support by sandbags. Total relief continued for a year afterwards and movement of the right leg, though limited by the fracture, was painless.

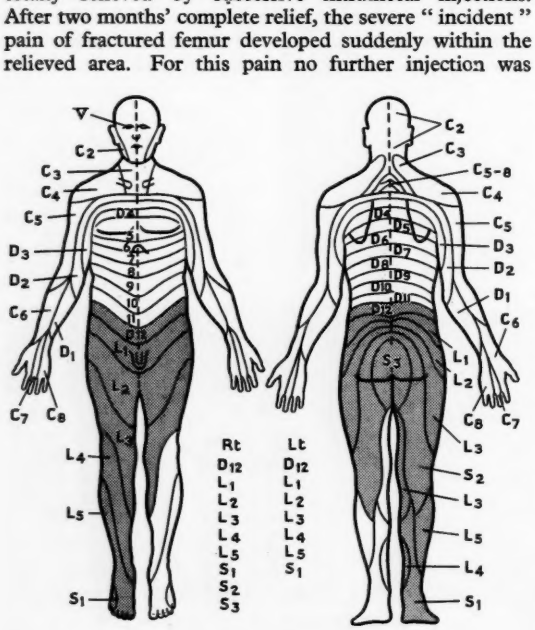

Fig. 2—Pain segment diagram in case 1.

CASE 2.—A woman of 59, with cancer of the cervix, was treated in 1953 by panhysterectomy and irradiation. Pain in the left groin began the following year at the site of a hard mass. Subarachnoid 1-in-20 phenol in glycerin at L1 was followed by a series of lumbosacral injections for both sides below D12. All sites must have been covered, because relief continued for eighteen months. A severe pain incident was relieved by rest only, and X-ray examination in November, 1955, showed advanced destruction of the bony pelvis with a fracture in the right pubis. Two weeks before she died in January, 1956, she was attempting to walk by pushing a chair in front of her.

CASE 3.—A woman of 25 with cancer of the right breast and vertebral collapse at D12–L1. After injection of 1-in-20 phenol for pain down both legs, " continuous " pain was eliminated but pain on movement remained. After immobilisation in spinal flexion for one month, relief continued for six months until she died.

CASES 4 and 5 had traumatic fractures after receiving intrathecal phenol, one for spasticity in disseminated sclerosis and the other for pain due to cancer of the cervix. Both had very brief pain, lasting only a few hours.

CASE 6.—A woman of 53, with adenocarcinoma of the breast, underwent radical mastectomy in October, 1957. Adrenalectomy in July, 1958, gave no relief and pain became violent. After 1·8 ml. of 1-in-20 phenol in glycerin from L1 level at 30°, pain subsided, and X-ray examination showed fracture of the left femur. Rest and fixation gave complete freedom from pain for eight months before she died.

CASE 7.—A woman of 53, with carcinoma of the right breast and spinal metastasis. Severe pain in the back began in February, 1957, and X-ray showed collapse of L1 and severe angulation to the left (fig. 3a). After irradiation to the spine and testosterone propionate she became pain-free until November, 1957. Intense pain then developed down the front and back of both thighs and extended to the feet. Fixation alone was found ineffective. Pain became intolerable in February requiring morphine and analgesia constantly. On Feb. 26, 1958, subarachnoid phenol was given for both sides at one session. This was only possible by strapping the patient in the anterior half of a plaster bed after she had had morphine. At D11–12 2 ml. of 1-in-20 phenol in glycerin was made to flow along the left side intrathecally along a caudal slope of 30°, thus probably covering 9 roots. After 20 minutes the patient was rotated in the plaster to lie on the right side and 1·5 ml. of phenol 1-in-20 in glycerin was allowed to flow caudally at 30°. Some 18 roots must have been influenced below D11. After this extensive injection the patient was supported, without the plaster, in spinal flexion and inclined to the right, to try to get the weight of the collapsed vertebræ off the roots, especially on the left. After two weeks she became pain-free and was discharged on March 14. She remained at home in the flexed position for two months, and then began to move without pain. In June, when she got up, spinal flexion had become stabilised, altering her balance somewhat, but walking became normal. Complete relief lasted for over two years (fig. 3b was taken in October, 1958), and then she was immobilised by a fracture of the femur.

A patient bedridden with spinal secondaries and intolerable pain was treated in June, 1958, by intrathecal injection, and after eight weeks was able to walk without pain for over a year so far.

2 advanced cases had similar treatment and relief, but walking was not possible.

2 patients were not relieved by subarachnoid phenol from the continuous pain, and incident pain persisted on movement.

Another 2 patients with spinal secondaries and pain in the legs from cancer of the breast are now pain-free and walking, following the same procedure, but 1 had adrenalectomy later.

Fig. 3—Case 7: (*a*) Angulation of spine in February, 1957; (*b*) patient in October, 1958, nearly a year after first onset of intense pain.

2 patients with cancer of the lung and spinal metastasis were relieved of pain in the arm by subdural injections followed by fixation in plaster.

The successful cases demonstrate that "reminder pain" fibres must have been eradicated completely, despite months of continuing cancerous invasion. The selection of these fibres by phenol enables the supervening severe "incident pain" to be clearly identified. Incident pain is due to direct stimulation of nerve-fibres or nerve-endings during sudden happenings such as fracture or vertebral collapse. Provided continuous pain had been relieved by phenol, absolute rest prevents friction or impact on the nerve and relieves the incident pain. The necessary period of rest after vertebral collapse is two months or more. Afterwards, since renewed movement did not provoke pain, processes of repair must have prevented stimulation of the nerve. Moreover, the spine became fixed in the adopted position of flexion. Conditions in the spine therefore closely resembled those of Pott's disease undergoing repair. In case 1, relief continued for a year after fracture, and the bony pelvis was found to be one soft mass, which could minimise stimulation and incident pain.

Continuous pain suggests stimulation of small C fibres, but it may itself increase with movement: it can be eliminated by phenol. Violent pain, indicating an "incident" or emergency, may be conducted along large A fibres.

Transmission of the Two Pains

How far these two pains are related to the two pains of external stimuli (Lewis and Pochin 1937) is hard to say. The effects of phenol have, however, thrown some light on this question. The greatest impact of 1-in-20 phenol intrathecally is on pain fibres not included with those for touch, tone, and movement, which are not demonstrably affected. Except when silver nitrate was included or too much phenol given no final cutaneous sensory changes were observed. When permanent relief ensues despite continuing penetration by growth these fibres must have been destroyed, and a different pain arising later from fracture might be taken to imply conduction along the only alternative pain path known—the A fibre group.

Using the timing tests of Lewis and Pochin (1938) with the copper cylinder at 63°C, varying results were obtained in 6 patients who had had intrathecal phenol. Sometimes there were curiously patchy changes in sensation: the effects shortly after intrathecal phenol in 2 cases showed one or two small areas with no sensation at all; all pain, swift and slow, had been abolished. All other areas gave a fast response of 0·4–0·6 sec. The second pain was recorded at 1·6 sec. from the ankle (75 cm. nerve length) except in the area analgesic to pinprick after injection.

The later result in other cases was usually abolition of the second pain where the area was relatively analgesic after injection of silver nitrate or a greater concentration of phenol. In 2 patients relieved without analgesia, the second pain was not abolished, and was recorded in 1·5–1·7 sec. from the ankle.

It seems that all fibres in the roots are affected immediately after phenol injections. The sensory effect wanes and after normal doses it is rare for sensory change to persist—an observation which coincides with the findings of Nathan and Scott (1958). In my series the timing tests show that with the smaller doses the second pain of Lewis and Pochin was unaffected. But, when greater amounts of phenol or silver nitrate were used, giving permanent relative analgesia, this second pain was abolished, suggesting that the small C fibres were eliminated. In general, however, subjective pain is relieved without inducing objective sensory changes. The whole phenol effect seems to be quantitative, with cutaneous C-fibre loss predominating.

Non-malignant Conditions

The risk of causing incapacity limited the use of intrathecal phenol in the treatment of non-malignant conditions (Maher 1957, Brown 1958). I often tried first the effect of extradural and trans-sacral injections, but for conditions with an existing disability intrathecal phenol was more clearly indicated. It was first used successfully for spasticity with flexor spasms (Maher 1957) and extended afterwards to other kinds of spasticity and parkinsonian rigidity. Phenol (1 in 20 in glycerin) was first used in doses up to 1 ml. Smaller doses, never exceeding 0·5 ml. at one time, have been given for pain with disability from arthritis, spondylitis, and failed disc operations (26 cases). Sensory and root reactions to phenol are much more pronounced in non-malignant states, so it is safer to grade the phenol doses by skin testing as described below. 0·3 ml. of 1-in-20 phenol once reached the "endpoint" of relative analgesia with retained touch sensation, and no more was injected.

Test solutions.—As a further guide before injecting lumbosacral sites, successive doses of cinchocaine hydrochloride ('Nupercaine'), gr. $^1/_{16}$ (0·004 g.), gr. $^1/_8$ (0·008 g.), and gr. $^1/_4$ (0·016 g.) in 1 ml. of glycerin, were injected intrathecally to give a temporary effect corresponding to 1-in-20 phenol. This precaution was first used for spasticity in 1956 and has been continued since to give a preview of the result. In 6 cases tested, gr. $^1/_{16}$ of cinchocaine seemed to match 1-in-20 phenol, but more results must be studied. The cinchocaine effect took much longer than that of phenol to become manifest.

For a given injection site and slope of the patient, the effect of cinchocaine may enable resistance of the nerve-roots to phenol to be predicted: in 2 recent cases no reaction to the test solution corresponded with resistance to phenol. For the treatment of pain, temporary relief from cinchocaine gr. $^1/_{16}$ indicated that 1-in-20 phenol would also give relief. Relief from cinchocaine gr. $^1/_8$ meant that the roots were hard to penetrate and relief less certain.

Certain inferences may be drawn from findings in cancer. For instance, abdominal pain from cancer has two main sources: (*a*) perineural metastasis; and (*b*) peristaltic pain from partial obstruction. (*a*) can be relieved by 1-in-20 phenol, but for (*b*) there was no

relief: this difference may be due to a different level of entry of fibres into the spinal cord. When stronger solutions were injected bowel movements diminished. It may be that the colics and the onset of the acute abdomen are incident pains arising from stimulation of large fibres and accompanying reflex rigidity. It is well known that tabetic patients may die from unrecognised acute abdominal conditions, because of the absence of pain; and similarly, a patient with cancer, who had had higher concentrations of phenol than usual, had no abdominal symptoms after perforation of a stercoral ulcer.

Present Techniques

The procedures now in use include the following methods.

The initial areas of pain are mapped on standard charts (fig. 2), on which any residual pain areas after injection are also recorded. These charts make it possible to place the injections more accurately and fig. 2 shows a case in which some 18 roots may need attention. Injections are continued until pain is totally abolished five days after injection. If pain returns after 3 or 4 root injections, the siting of the injections may be inadequate or more phenol may be needed.

Control of Phenol Injection by Sensory Changes

At the dorsolumbar level (intrathecal 1-in-20 phenol in glycerin), sensory effects from an initial 0·3 ml. give a good idea of the position of the needle. For D12–L1 injections, changes in sensation should then immediately correspond with the segments reached. The bevel of the needle should be directed downwards towards the required roots in the lateral lumbar position, with a slight caudal slope. After this first dose, paræsthesiæ should soon be felt in the groin or thigh. If not, a slight and temporary increase in caudal slope may evoke them. If, however, the initial sensory symptoms appear in the sciatic group, particularly the foot or leg, injection should be abandoned, and attempted again a day or so later. Sensory symptoms in the foot indicate that the needle is too far over to the unaffected side and that phenol is flowing over the cauda equina. The nervous mechanism for micturition may be damaged if phenol covers the lowest part of the cord.

The immediate sensory symptoms induced by intrathecal phenol can be matched against the final result. The order of events is as follows: First, instantaneous relief is common, followed by tingling and paræsthesiæ at the appropriate site. There follows diminished sensation to pinprick and scratch, *compared with the opposite side.* After further doses, pinprick and scratch sensation may vanish, but light touch is unaffected. Later, light touch diminishes compared with the opposite side. Finally, light-touch sensation and scratch may cease and the limb become awkward. If this is permanent, movement of the limb may be impaired.

This sensory-gradation method of controlling injections is based on the fact that light touch is conducted by large fibres and, if it is unaffected, the other large fibres for tone and movement are also intact. A dose of 1 ml. may be insufficient for some patients and too much for others. A total of 1·2 ml. or more can sometimes be used, but, in 3 instances, 0·5 ml. was the maximum possible dose.

It is very necessary, therefore, that tests for sensation should be repeated after each 0·3 ml. has been injected, and *light touch must not be affected.* Sensation in the groin is particularly important during L1 injections.

The " endpoint " for stopping the injection is diminution or loss of scratch and pinprick, with light touch intact; and the injection can be continued until this stage is reached.

For injection at L4–5 for pain in the lower limb and sacral segments similar tests are carried out, and usually 0·5–0·75 ml. is the total required. Larger doses may reach the 2nd, 3rd, and 4th sacral units.

During the study of 20 cases of disseminated sclerosis by Dr. L. A. Liversedge and myself, fear of damaging the sacral nerves, and so causing urinary dysfunction, led us to adopt covering agents. Before injecting phenol in glycerin at L2–3, subarachnoid puncture at L5–S1 was used to introduce either pure myodil or glycerin alone over the sacral roots. This prevented urinary dysfunction in 5 out of 6 cases with existing disability of micturition. A day or two's temporary incontinence followed injection in these circumstances.

Other Intrathecal Injections

For *pain in the rectum* and bottom of the coccyx, such as may follow the abdominoperineal operation, subarachnoid puncture is done at L5–S1 with the patient vertical; and he then lies on the side of greatest pain, with the trunk elevated to 20° with the horizontal. 0·7 ml. of 1-in-20 phenol in glycerin is allowed to flow gently down the lateral dura to the end of the dural sac. The patient is then gradually raised to the vertical. The phenol must not be allowed to diffuse through *all* the sacral roots because that would cause retention. This was the disadvantage of the original vertical-drop method (Maher 1957). After a few seconds, the patient is turned over to the opposite side at 15° elevation.

For *upper abdominal and lower thoracic pain* subarachnoid puncture at D9–10 is preferable. The patient lies with the pelvis elevated to 20°. 0·5 ml. of 1-in-20 phenol in glycerin is used as the initial solution. *If there is no effect on the lower limbs* 1·5–3 ml. of 1-in-15 phenol can be slowly injected. Silver nitrate gr. $^1/_{100}$ with 1-in-25 phenol is an alternative.

Extradural Injections

For *cervical and upper dorsal pain* puncture and injection are performed with the patient sitting upright. When cerebrospinal fluid flows, the needle is withdrawn steadily 1 mm. at a time, until the flow of C.S.F. nearly ceases. 0·5 ml. 1-in-20 phenol in glycerin is then used as a trial. If tingling is felt in the back below the needle, the phenol is still intrathecal and is flowing downwards. If there are no symptoms 1-in-15 phenol can be slowly and carefully injected. If air is also injected at the same time the phenol descends slightly and affects the upper dorsal roots, which may be involved in cancer of the lung. Recently, this method has produced improvement in 4 out of 8 cases of lung cancer.

Trigeminal Pain in Cancer

By using Harris' route over the sigmoid notch of the mandible (Harris 1937) and inverting the head so that the orbit is higher than the mastoid (fig. 4), 1–2 ml. of 5% aqueous phenol will flow towards the foramen ovale at a needle depth of $1^1/_4$ in. The foramen ovale should *not* be penetrated. The injection may be repeated if necessary. 18 out of 24 cases were relieved. Injection of phenol in glycerin is difficult; it was used until recently. No sensory changes have been noted.

Factors influencing Final Results

Intrathecal phenol is effective for lumbosacral and dorsal sites below D3: relief was complete in 61 out of 81 cases. Recently, using the gradation method of injection control, relief was attained in 12 out of 14 cases. Above D3 intrathecal phenol is not used. Subdural phenol gives better results for cancer of the lung; originally only 1 in 5 were relieved, but recently 4 out of 8 patients were freed from pain by the new methods.

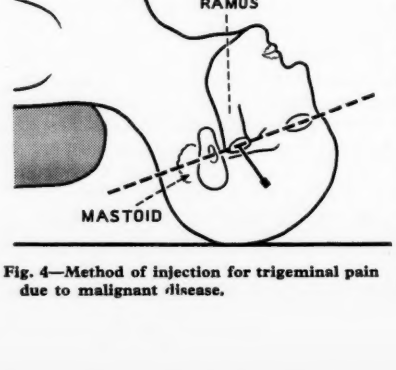

Fig. 4—Method of injection for trigeminal pain due to malignant disease.

Originally patients were referred for treatment late in their illness, and complete resistance to phenol often corresponded to growth around the ganglia and roots (the "sheltering" phenomenon) (Maher 1957). Now with earlier treatment a gradual increase in resistance is noted as the disease advances. Phenol is very potent with small areas of early pain, and sometimes 0·3 ml. of 1-in-20 phenol was the maximum dose permissible. Pre-existing root damage by cancer may be responsible for this effect.

Glycerin, used for the early injections in 1955, is still the conveyor of choice for all subarachnoid injections. Myodil tends to protect the roots and interfere with any later injections that may be needed.

1 ml. of phenol will cover only three roots at a time. In fig. 2, 9 or 10 roots on each side need attention at three or four sessions. Further injections can be given later. Provided relief is progressive, the effect on morale is good. If phenol-treated segments do not respond, phenol/silver-nitrate mixture can be used. The aim is to continue injections until all pain has, if possible, been relieved.

Phenol Mixtures with Silver Nitrate

At lumbosacral sites only, 1-in-25 phenol in glycerin mixed with silver nitrate gr. $^1/_{100}$ or gr. $^1/_{80}$ was used when phenol alone was not enough. Above lower dorsal level it was considered unsafe (Maher 1957). After the experience of Nathan and Scott (1958), it was tested further at various concentrations for lumbosacral sites.

In 21 cases gr. $^1/_{30}$ (0·0022 g.) of silver nitrate per ml. of agent gave relief in 15 resistant cases. In 6, severe meningeal symptoms followed the injection. In 33 cases gr. $^1/_{100}$ (0·0006 g.) of silver nitrate per ml. gave relief in 23, with slight meningeal symptoms in 1. In 18 cases gr. $^1/_{150}$ (0·0004 g.) silver nitrate per ml. gave relief in 13 with no accompanying meningeal symptoms. There were no fatalities among patients treated with silver nitrate. With the greater concentration, gr. $^1/_{30}$ (0·0022 g.) meningeal symptoms were alarming in 2 patients, and arose within a few minutes of injection: pain began at the site and spread headwards, requiring morphine.

The most effective concentration was gr. $^1/_{100}$ (0·0006 g.) per ml. of 1-in-25 phenol in glycerin. As an additional precaution 0·5 ml. was sometimes injected as a trial. After 20 minutes, in the absence of symptoms, the remaining 0·5 ml. was added. Morphine (gr. $^1/_6$) half an hour before injection is of value.

It is important to keep the patient lying still in the injection position for an hour afterwards: this localises the agent to the required roots. Attacks of pain decrease with time and die out after a week.

Of the 25 lumbosacral cases unrelieved by phenol alone, 15 were free from pain after phenol and silver nitrate (Maher 1957). Silver nitrate has become less necessary now that cases are referred earlier. Moreover, phenol alone is made more effective by the method of gradation described above. There is no doubt, however, that the phenol/silver-nitrate mixture is the most powerful agent for relief, and gr. $^1/_{100}$ per ml. was found to be safe.

Preparation of Phenol/Silver-nitrate

To prepare a solution containing silver nitrate gr. $^1/_{100}$ (0·0006 g.) per ml. of 1-in-25 phenol in glycerin (usual dose 1 ml.), 24 ml. of sterilised glycerin is added to a 30 ml. amber 'Clinibrittic' bottle, washed and sterilised by dry heat at 150°C for one hour.

Solution 1.—1 g. of phenol crystals are added to this 24 ml. of sterile glycerin. A sterile rubber cap is fitted.

Solution 2.—Ampoules of silver nitrate containing gr. 5 (0·3 g.) in 6 ml. of water for injection are prepared and autoclaved.

Take 0·3 ml. of solution 2 and add to solution 1. Add 0·7 ml. further of water for injection, to bring the total volume to 25 ml.

Conclusion

Specialists in cancer and orthopædic surgery have long noted that immobilisation often brings relief of pain in malignant disease. I have attempted to explain this in terms of the type of pain transmitted by different fibres, and to show how the removal of more slowly conducted pain can assist in relief of the swift emergency pain. With pain abolished, patients seemed to live longer, and repair in the spine was sometimes sufficient for some months' walking. Perhaps irradiation and androgens were given more time to act. Measures such as irradiation, adrenalectomy, and androgens have prolonged life, but the first essential is relief of pain, and here injection methods may aid surgical procedures.

I am deeply indebted to Sir Geoffrey Jefferson and Mr. R. T. Johnson for their encouragement and advice. My thanks are also due to the Manchester Regional Hospital Board for their grant and for the establishment of a Pain Relief Centre. I should like to thank also Dr. and Mrs. J. Starkie, Mr. and Mrs. J. Edmonds, and Mrs. E. Ashworth. I acknowledge too the great assistance I received from Dr. J. Shrigley in the study of the pathological findings.

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INTERMITTENT POSITIVE-PRESSURE RESPIRATION AND THERAPEUTIC BRONCHIAL LAVAGE IN INTRACTABLE STATUS ASTHMATICUS

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ONLY in recent years has it been realised that death from uncomplicated bronchial asthma is not rare (Earle 1953).

Probably there are about 400,000 asthmatics in the United Kingdom in any one year (Stocks 1949). The reports of the Registrars General infer that each year about 3000 people die directly owing to bronchial asthma (Robertson and Sinclair 1954). Westlund and Hougen (1956) gave a mortality of 12·5% from "pure" asthma in a follow-up survey of the 327 patients seen at the Ulleval Hospital, Oslo, between 1917 and 1936; Williams and Williams (1949) followed up 64 cases of bronchial asthma for from seven to twelve years and found that 17·2% had died from asthma.

While opinions differ as to the relative importance of the several factors operating in asthmatic bronchial occlusion, all workers emphasise the predominant role of viscid mucus as the final cause of asphyxia. In a review of reports published between 1922 and 1951 (Earle 1953) only 6 of the 90 cases cited did not show "the bronchial tree plugged with sticky mucus".

As Houston et al. (1953) point out: "There is no doubt that the majority of patients diagnosed clinically as being in status asthmaticus recover, and presumably in these patients there is only partial bronchial plugging with added bronchial spasm which in time becomes amenable to treatment." Recent accounts include necropsy reports of at least 6 patients who died in status asthmaticus while on cortisone, and all reports refer to typical

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bronchial mucus plugging (Davies and Williams 1955, Houston et al. 1953, Robertson and Sinclair 1954, Savidge and Brockbank 1954).

Since February, 1959, there have been 3 consecutive deaths from uncomplicated status asthmaticus in Salisbury General Infirmary, despite energetic orthodox treatment which included steroid therapy in each case. In all 3 cases necropsy revealed thick bronchial mucus plugging. The following two cases are reported to indicate what seems to be a successful line of treatment in the otherwise hopeless case of status asthmaticus.

Case-records

Case 1.—A woman, aged 40, had had bronchial asthma for ten years. Her general practitioner stated that she was "a nervous, tense, and timid person who fears to have another child and is afraid of being shut in". The total duration of her attack was five days, of which the last two days had been spent in hospital.

Aug. 27, 1959: noon.—Admitted with severe dyspnœa, not cyanosed, chest expansion poor, much audible wheeze, percussion note resonant, pulse-rate 140 per minute, blood-pressure (B.P.) 150/100 mm. Hg. The following treatment was started: intramuscular chlorpromazine 100 mg., intramuscular promethazine 100 mg., intramuscular pethidine 50 mg. six-hourly; oral prednisone 15 mg. six-hourly; and 1 megaunit soluble penicillin eight-hourly.

3 p.m.—Well sedated.

7.30 p.m.—Much deterioration over past twenty minutes: cyanosed and grey, wheezing stridently, pulse-rate 160, B.P. 90/70. 0·5 g. thiopentone and 100 mg. succinylcholine given intravenously and endotracheal intubation performed with cuffed no. 10 Magill tube. Light ether anæsthesia maintained with 2 litres oxygen per minute, from Boyle's machine.

8 p.m.—Intravenous drip set up with 100 mg. hydrocortisone and 500 mg. succinylcholine in 500 ml. physiological saline solution. Positive-pressure respiration maintained at rate of about 10 per minute. Colour pink and wheeze apparently less; B.P. 100/70.

10.30 p.m.—No expansion of chest on positive pressure; B.P. 80/50. Tube removed and found to be blocked with thick mucus. Another Magill tube inserted and many plugs of mucus aspirated, with Tiemann's coudé catheter attached to oxygen sucker. Chest movements satisfactory after this procedure.

Aug. 28: 12.30 a.m.—Wheeze worse, pulse-rate 140, B.P. 90/60.

1 a.m.—No chest expansion on positive pressure. Trypsin (calcium salt) 50 mg. in 10 ml. physiological saline flushed down endotracheal tube, after attempted aspiration unsuccessful. Much mucus aspirated one minute later. Chest movements satisfactory.

4 a.m.—No chest expansion on positive pressure. Trypsin lavage repeated with similar effect.

9 a.m.—General condition much improved and wheeze apparently decreasing; chest expansion good; B.P. maintained at 140/90.

Noon.—Progress maintained; wheeze almost gone.

5 p.m.—Intravenous drip discontinued and spontaneous respiration allowed to recommence.

6 p.m.—Anæsthesia discontinued and endotracheal tube removed. No wheeze apparent.

7 p.m.—The patient took a light supper.

The Magill tube had been deflated every four hours. Two litres physiological saline, 400 mg. hydrocortisone, and 2000 mg. succinylcholine had been given over twenty-four hours.

Subsequent progress was uneventful; chest radiograph was normal. The patient was discharged on Sept. 16.

Case 2.—This patient, a man aged 64, had "never had a day's illness" until three years ago when he contracted influenza; a "nervous breakdown" followed, which had not been improved by his daughter narrowly escaping a second divorce in the U.S.A. He had noticed that the asthma came on when he got "stirred up". The total duration of his attack was four days, of which the last two days had been spent in hospital.

Oct. 2, 1959: 11.30 p.m.—On admission the patient was anxious, dyspnœic, not cyanosed; poor chest expansion, percussion note resonant, severe wheeze, pulse-rate 100, B.P. 120/80. Aminophylline 0·75 g. administered intravenously with good effect; chlorpromazine and promethazine 100 mg. given intramuscularly. Penicillin 1 megaunit eight-hourly started.

Oct. 3: 1.45 a.m.—General condition deteriorated; restless and cyanosed; B.P. 100/70. Prednisolone 50 mg. given intravenously with good effect.

3.45 a.m.—General condition somewhat improved; no cyanosis but restlessness persisted. Chlorpromazine and promethazine 100 mg. given intramuscularly.

5.45 a.m.—Improvement maintained; no cyanosis, B.P. 120/80. Prednisolone 25 mg. given intravenously.

8 a.m.—Patient collapsed; B.P. 80/60. Thiopentone 0·5 g. and succinylcholine 100 mg. given intravenously, and cuffed endotracheal Magill tube (no. 10) inserted. Intravenous drip set up with 500 ml. physiological saline solution, 750 mg. succinylcholine, and 25 mg. prednisolone. Continuous anæsthesia started with 2 litres oxygen and 4 litres nitrous oxide per minute, from Boyle's machine. Positive-pressure respiration maintained at rate of about 10 per minute.

8.20 a.m.—General condition still poor; much mucus aspirated with Tiemann's coudé catheter connected to oxygen sucker. Chest movement improving; pulse-rate 140, B.P. 100/70. Cyanosis relieved by aspiration.

9.30 a.m.—No cyanosis, B.P. 130/80.

10.40 a.m.—No chest expansion on positive pressure, cyanosis, B.P. 80/60. Trypsin (calcium salt) 50 mg. in 10 ml. physiological saline solution flushed down endotracheal tube, and after one minute much mucus aspirated. It was very difficult to get the mucus out of the Tiemann's catheter into the sucker bottle. Cyanosis relieved by aspiration and chest movement satisfactory.

10.50 a.m.—B.P. 150/100.

12.15 p.m.—Considerable resistance to inflation; much thick mucus aspirated.

2.30 p.m.—Condition satisfactory; no further cyanosis. Respirations maintained at about 10 per minute.

5.50 p.m.—Cyanosis and cessation of chest movement. Trypsin lavage repeated as above with aspiration of copious mucus, relief of cyanosis, and return of chest expansion.

9.15 p.m.—Aspiration of much mucus.

10.30 p.m.—Succinylcholine discontinued, but prednisolone maintained.

Oct. 4: 12.5 a.m.—Wheeze very slight, chest expansion excellent.

12.30 a.m.—Suction of much mucus and also gastric contents from oronasopharynx. Spontaneous respiration of good amplitude and about 15 per minute. B.P. 130/80.

1 a.m.—Anæsthesia discontinued and oxygen only given.

1.30 a.m.—Vomiting of dark brown juice; stomach aspirated with œsophageal tube and 500 ml. fluid removed. Endotracheal tube removed.

2.10 a.m.—Patient regained consciousness.

2.30 a.m.—Patient responding to command to cough with great difficulty but with good effect. Pronounced cyanosis and wheeze attended these efforts.

3 a.m.—No cyanosis or wheeze. Respiration-rate 14 per minute.

The Magill tube had been deflated every four hours. Between 11 P.M. on Oct. 2 and 2.10 A.M. on Oct. 4, 3 litres of physiological saline solution, 3500 mg. succinylcholine, and 135 mg. prednisolone were given. Subsequent progress in hospital was uneventful; the patient remained apyrexial, the

chest radiograph was normal, and sputum culture was negative. The patient was discharged on Oct. 13.

Discussion

The prognosis in status asthmaticus is difficult to assess, but the manifestations and consequences of gross respiratory obstruction cannot long continue unchecked. Bronchial occlusion in asthma is initially reversible by bronchodilator therapy, but when death occurs in this disease it is chiefly due to mucus obstruction. Orthodox treatment usually ends the acute attack of status asthmaticus, but when such treatment is ineffective the relief of respiratory obstruction may become urgent. As asthmatic respiratory obstruction increases, the therapeutic problem becomes one of ventilation in general rather than expiration in particular. In the moribund patient the potential hazards of assisted respiration are less immediate than the actual risks of unrelieved anoxia. Both " air-trapping " and " airway collapse " can occur with mechanically assisted respiration and may lead to respiratory and circulatory failure (*Lancet* 1959); but that neither is inevitable, over a period of twenty hours, has been shown in this paper. Aerosol therapy and bronchoscopic suction are of proven value in status asthmaticus, but they are not always effective (Savidge and Brockbank 1954, Robertson and Sinclair 1954). In the later stages of status asthmaticus, aspiration of mucus involves reaching the main bronchi; and, when the conscious efforts of the patient are insufficient adequately to inspire, expire, or expectorate, anæsthesia is necessary. In the extreme case of status asthmaticus, continuous counteraction of the twin hazards of mucus accumulation and ventilatory insufficiency may be necessary (Hugh-Jones 1958).

Summary

3 consecutive deaths from uncomplicated status asthmaticus, despite intensive orthodox measures which included steroid therapy, prompted a search for a more satisfactory treatment.

2 patients in status asthmaticus, moribund despite steroids, with chest fixation, cyanosis, and systolic hypotension, were successfully treated by continuous intermittent positive-pressure respiration under anæsthesia, using a Boyle's machine.

Regular aspiration was practised, using a Tiemann's coudé catheter connected to an oxygen sucker. In both patients endobronchial lavage with trypsin enabled aspiration, previously ineffective, to be satisfactorily performed. The rapidity with which the mucus was subsequently aspirated suggests that the effect of trypsin was not due to its digestive action.

This method seems worthy of further trial in otherwise intractable status asthmaticus.

I should like to thank Dr. E. M. Collings and Dr. S. M. Gorringe and many nurses of the Salisbury General Infirmary for their help; and Dr. J. H. Gubbin and Dr. R. G. M. Longridge, under whose care these patients were admitted, for their encouragement.

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FŒTAL MORTALITY IN ESSENTIAL HYPERTENSION

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OPINIONS differ on the highest level of blood-pressure that can be regarded as normal during the early weeks of pregnancy. The commonly accepted figures of 140 mm. Hg systolic and 90 mm. diastolic have been disputed, notably by Browne (1951) whose standard is 120/80 mm. About 1% of women have a blood-pressure of 140/90 mm. or over during the early weeks.

It is generally believed that hypertension is associated with an increased fœtal mortality. Some of the stillbirths are due to premature separation of the placenta, while others have been attributed to placental insufficiency (Browne and Veall 1953, Walker and Turnbull 1953, MacKay 1957, Paine 1957, Russell et al. 1957). Browne and Dodds (1942) found that only 32% of patients who began pregnancy with blood-pressures of 150/100 or over gave birth to living children.

After observing several patients who started with blood-pressures far in excess of this, and being surprised to find that the outcome was usually satisfactory, I decided to reappraise the fœtal prognosis in the light of present-day management.

Selection and Care of Patients

The series comprised 73 patients in whom the blood-pressure was 150/100 or over before the twentieth week of pregnancy.

It was not very easy to find cases which satisfied these criteria, since large numbers of hypertensive patients were not seen until after the twentieth week.

The series was drawn from the patients booked for delivery in the Nottingham Hospital for Women during the three years 1955–58, and in Saint Mary's Hospital, Manchester, during the preceding three years. A blood-pressure level of 150/100 was taken as the standard, so that the series could be compared with that of Browne and Dodds. No case was included if there was any reason to suspect that the initial reading was fallacious or that the hypertension was transient. Often the blood-pressure was very much higher than 150/100.

2 of the patients had chronic nephritis and have been excluded.

The first line of treatment was insistence on long periods of rest in bed, and usually this involved admission to hospital and sedation with phenobarbitone. Antihypertensive drugs, such as mecamylamine or pentolinium, were prescribed in a few severe cases.

Induction of labour before term was favoured, and pregnancy was never allowed to progress beyond the expected date of delivery. Artificial rupture of the membranes was performed in 26 cases (37%) and cæsarean section in 15 (21%), the indications being:

Severe pre-eclampsia	6	Diabetes mellitus	1
Severe hypertension	3	Previous cæsarean section (tender scar)	1
Elderly primigravidæ	2		
Contracted pelvis	1	Prolonged labour	1

Results

1 pregnancy was terminated at twenty weeks because the blood-pressure was 230/150, and because there were retinal and renal changes. There were 4 stillbirths and 1 neonatal death. The total fœtal loss was therefore 6 (8%).

The average weight of the infants, including the stillbirths, was 6 lb. 10 oz. All the infants which were lost weighed less than 5 lb.

30 patients (42%) developed œdema or albuminuria or both. The neonatal death, and 3 out of the 4 stillbirths, were in this group. There was only 1 case of accidental hæmorrhage and this accounted for 1 stillbirth. There were no cases of eclampsia or cerebral hæmorrhage and no maternal deaths.

Comment

3 out of the 4 stillbirths and the 1 neonatal death were in patients who developed albuminuria or œdema or both—and this at a stage of pregnancy (before thirty-three weeks) when there was reluctance to interfere because of the immaturity of the fœtus. The prevention of this complication is therefore of the first importance.

It may be of value to compare the results of Browne and Dodds, published in 1942, with those of the present series, and to consider the possible reasons for the improved prognosis. Of their 239 patients with hypertension in pregnancy, 25 had a blood-pressure of 150/100 or over before the twentieth week. In these 25 cases, only 8 infants survived (32%). No woman with an initial systolic pressure of 180 mm. or over bore a live child.

In the present series of 71 patients in whom the blood-pressure before the twentieth week was 150/100 or over, 65 infants survived (92%). In 15 cases the initial systolic pressure was 180 mm. or over and in 12 of these a live child was born.

It seems clear that with modern obstetric care a better fœtal prognosis can now be given in these hypertensive cases. The work of Browne and Dodds, by drawing attention to the importance of hypertension and proposing principles for its management, was probably the starting-point of a steady improvement. Emphasis was placed on mental and physical rest, induction of labour before term, and cæsarean section in selected cases.

The wider application of these three principles—particularly the more frequent use of cæsarean section—was probably the main reason for the good results in our series. Progress in the management of prematurity has also contributed to the improvement.

Summary

A series of 71 patients in whom the blood-pressure was 150/100 mm. Hg or over in early pregnancy is analysed. The fœtal mortality is much lower than in a similar series published in 1942, and the difference is largely attributable to better obstetric care.

I am indebted to the consultants of Saint Mary's Hospital, Manchester, and the Nottingham Hospital for Women, for permission to publish these observations; and to Prof. C. S. Russell for advice in writing the paper.

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Preliminary Communication

N-TERMINAL-AMINOACID PATTERN IN NORMAL AND PATHOLOGICAL HUMAN SERUM

THE quantitative determination of N-terminal amino-acids of some serum proteins has already been described.[1] The results prompted us to study the N-terminal-amino-acid pattern of human serum proteins. We here report preliminary data concerning the N-terminal-aminoacid pattern of normal serum compared with that from patients with dysproteinæmia.

MATERIALS AND METHODS

Serum was taken for investigation from nine normal subjects, four patients with macroglobulinæmia Waldenström, four myeloma patients (two of whom had cryoglobulins), and two patients with disseminated lupus erythematosus. The clinical findings in all cases were typical, and the diagnoses were all made by J. W.

The N-terminal analyses were usually performed on 1 or 2 ml. of serum previously dialysed against 0·05 *M* phosphate buffer (pH 8·0) according to a recently described modification of the Edman phenyl-thiohydantoin method.[1 2]

Paper electrophoresis was performed by the method of Laurell et al. [3] Protein content was determined by a biuret method and by a micro-Kjeldahl procedure.

RESULTS

Table I shows the N-terminal-aminoacid pattern of the serum proteins from nine normal subjects. The following N-terminal aminoacids were consistently demonstrated: alanine, aspartic acid, glutamic acid, glycine, leucine (or isoleucine), serine, and valine. Using this method, leucine and isoleucine cannot be distinguished, and arginine, histidine, and cysteine (or cystine) cannot be determined.

The quantitative N-terminal composition of the serum was similar in all the normal subjects. The total amount of N-terminals varied between 8·04 and 9·44 millimols per 100 g. protein nitrogen. Aspartic acid predominated, comprising about 67% of the total N-terminal aminoacids.

1. Eriksson, S., Sjöquist, J. *Clin. chim. Acta*, 1960 (in the press).
2. Sjöquist, J. *Biochim. biophys. Acta*, 1960 (in the press).
3. Laurell, C. B., Laurell, S., Skoog, N. *Clin. Chem.* 1956, **2**, 99.

TABLE I—THE N-TERMINAL-AMINOACID PATTERN IN NORMAL HUMAN SERUM
(millimols per 100 g. protein nitrogen)

N-terminals	Serum specimens									Range	Mean	% of total N-terminals
	1	2	3	4	5	6	7	8	9			
Alanine	0·28	0·31	0·49	0·31	0·32	0·41	0·43	0·29	0·35	0·28–0·49	0·35	4·1
Aspartic acid	5·25	5·43	5·50	5·64	6·55	5·90	5·95	5·45	6·01	5·25–6·55	5·74	67·1
Glutamic acid	1·14	1·02	1·05	0·88	1·09	0·85	1·15	0·85	1·06	0·85–1·15	1·01	11·8
Glycine	0·32	0·25	0·23	0·16	0·28	0·25	0·42	0·25	0·30	0·16–0·42	0·27	3·2
Leucine } Isoleucine }	0·31	0·27	0·37	0·18	0·23	0·36	0·23	0·36	0·36	0·18–0·37	0·30	3·5
Serine	0·36	0·46	0·31	0·47	0·56	0·32	0·37	0·32	0·33	0·31–0·56	0·39	4·6
Valine	0·38	0·51	0·53	0·43	0·41	0·58	0·40	0·58	0·61	0·38–0·61	0·49	5·7
Sum	8·04	8·25	8·48	8·07	9·44	8·67	8·95	8·10	9·02	8·04–9·44	8·55	100

TABLE II—THE N-TERMINAL AMINOACIDS OF PATHOLOGICAL HUMAN SERUM
(millimols per 100 g. protein nitrogen and % of total N-terminals)

Diagnosis	Macroglobulinæmia Waldenström				Myelomatosis				Disseminated lupus erythematosus		Mean normal values
Case no.	1	2	3	4	5	6	7	8	9	10	
N-terminals:											
Alanine	2·95 (33·2%)	0·12 (2·3%)	0·16 (2·8%)	0·31 (3·5%)	0·31 (7·0%)	0·20 (2·7%)	0·39 (4·7%)	0·13 (2·3%)	0·30 (4·6%)	0·40 (4·8%)	0·35 (4·1%)
Aspartic acid	2·27 (25·5%)	1·48 (28·4%)	4·67 (82·0%)	4·76 (53·8%)	0·99 (22·3%)	5·15 (68·5%)	2·36 (28·6%)	4·50 (80·7%)	3·20 (49·1%)	3·84 (46·4%)	5·74 (67·1%)
Glutamic acid	2·40 (27·0%)	3·01 (57·8%)	0·44 (7·7%)	1·87 (21·2%)	0·34 (7·7%)	0·67 (8·9%)	2·40 (29·1%)	0·37 (6·5%)	1·78 (27·3%)	2·13 (25·8%)	1·01 (11·8%)
Glycine	..	..	..	0·40 (4·5%)	0·33 (7·3%)	0·33 (4·4%)	0·39 (4·7%)	0·17 (3·0%)	..	0·35 (4·2%)	0·27 (3·2%)
Leucine } Isoleucine }	0·33 (3·7%)	0·14 (2·7%)	..	0·43 (4·9%)	0·20 (4·5%)	0·31 (4·1%)	0·28 (3·3%)	0·07 (1·3%)	0·24 (3·7%)	0·89 (10·8%)	0·30 (3·5%)
Serine	0·43 (4·8%)	0·25 (4·8%)	0·30 (5·3%)	0·47 (5·3%)	1·98 (44·6%)	0·41 (5·5%)	1·94 (23·5%)	0·23 (4·1%)	0·52 (8·0%)	0·66 (8·0%)	0·39 (4·6%)
Valine	0·53 (5·8%)	0·21 (4·0%)	0·13 (2·3%)	0·60 (6·8%)	0·29 (6·5%)	0·44 (5·9%)	0·50 (6·1%)	0·11 (2·0%)	0·48 (7·4%)	..	0·49 (5·7%)
Sum	8·90	5·21	5·70	8·84	4·44	7·51	8·26	5·58	6·52	8·27	8·55

Table II shows the corresponding N-terminal amino-acid patterns from the pathological serum specimens. These N-terminal patterns differ significantly from those of the normals. Thus, only the serum from case 1 had a high content of N-alanine. In all the cases studied N-aspartic acid was more or less reduced. N-glutamic acid showed the most variable values: in cases 1, 2, 7, and 10 it was increased; in cases 3, 5, 6, and 8 it was decreased; and in cases 4 and 9 it was moderately increased. N-glycine could not be detected in four serum specimens (cases 1, 2, 3, and 9), and N-leucine (or isoleucine) was not detected in case 3 but was increased in case 10. The N-serine content was markedly high only in cases 5 and 7. N-valine was within or near

TABLE III—THE PROTEIN DISTRIBUTION OF PATHOLOGICAL SERA AS DETERMINED BY PAPER ELECTROPHORESIS
(g. per 100 ml. serum)

Case no.	Total protein	Albumin	α_1	α_2	β_1	β_2	γ
1	7·80	2·34	0·35	0·56	0·33	0·27	3·92
2	13·50	3·54	0·32	0·47	0·30	0·18	8·69
3	8·30	2·24	0·27	0·34	0·25	0·20	5·01
4	8·64	4·58	0·35	0·60	0·55	0·19	2·37
5	12·10	2·32	0·50	0·61	0·59	0·31	7·77
6	11·50	3·27	0·35	0·58	0·38	0·26	6·69
7	6·66	2·50	0·42	0·66	0·40	0·30	2·38
8	10·62	1·63	0·26	0·40	0·37	0·29	7·67
9	6·70	2·29	0·29	0·53	0·39	0·55	2·66
10	6·00	2·05	0·66	0·96	0·43	0·34	1·57
Normal range	7·64–6·60	4·89–4·17	0·41–0·27	0·63–0·43	0·61–0·39	0·44–0·26	1·08–0·65

normal values in all except case 10, where it was absent. The total amount of N-terminal aminoacids was appreciably reduced in cases 2, 3, 5, 8, and 9.

The paper electrophoreses of the pathological serum specimens (table III) showed various degrees of hypergammaglobulinæmia combined with striking hypoalbuminæmia, except for case 4, which had a normal albumin value.

DISCUSSION

Most previous investigations have been concerned with determining the N-terminal aminoacids of a single serum-protein or fraction (see Eriksson and Sjöquist[1]). Human albumin has N-terminal aspartic acid. Human γ-globulin contains N-aspartic acid, N-glutamic acid, and a small amount of N-serine. N-aspartic acid and N-glutamic acid, as well as N-serine and N-threonine, have been identified in different lipoprotein fractions.[4] As to other serum proteins, little information is available. Transferrin has valine as an N-terminal aminoacid.[5]

4. Rodbell, M. *Science*, 1958, **127**, 701.
5. Putnam, F. W. *ibid.* 1955, **122**, 275.

Preliminary experiments in this laboratory on an α-globulin fraction (obtained by chromatography on D.E.A.E.-cellulose) have shown that it contains several N-terminal aminoacids (alanine, aspartic acid, glutamic acid, glycine, leucine or isoleucine, and serine). The N-terminal-aminoacid patterns of whole normal serum reported here (table I) agree well with the above findings on individual serum proteins.

The diagnostic value of the N-terminal-aminoacid pattern cannot yet be evaluated as only few cases have been examined, and even patients with the same clinical diagnosis had various N-terminal aminoacids. It should be noted that sera with almost identical electrophoretic patterns may have strikingly divergent N-terminal amino-acid patterns, and therefore each serum specimen must contain proteins of different chemical structure. The low content of N-aspartic acid in some cases may be explained by the hypoalbuminæmia. This study, however, was not concerned with defining which serum-protein fraction contained the measured N-terminal aminoacid, although this is being investigated. Studies on several abnormal protein fractions from patients with dysproteinæmia have recently been published by Putnam.[6]

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"... The great challenge at the older ages is how to keep a person fit until he dies, functioning as a dynamic unit in the population and contributing to society so that he can maintain his sense of value and dignity. It is quite possible that much of chronic disease could be eliminated if physicians knew how to recognise various levels of wellness. If, as seems certain, in the lower levels of wellness exist the precursors of future illness, it becomes increasingly important that we be able to recognise the levels of wellness. What is top-level wellness? How can one recognize the persons possessing it at the various ages? Can therapy be designed to raise the individual's level of wellness?"—HALBERT L. DUNN, M.D. *Journal of the National Medical Association*, 1957, **49**, 225.

Medical Societies

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

THE 80th annual congress of the society was held in London on March 31 to April 2, under the presidency of Mr. R. C. DAVENPORT. Some of the contributions are summarised below.

The Visually Defective Infant

Mr. F. W. LAW discussed the question of whether an infant can see or not; it was usually hard to examine the infant's fundus fully, unless a general anæsthetic was given, and even then it was not possible to be dogmatic about sight unless there was a definite and gross fundus lesion. There is also the question of associated mental defect, which may mask the signs of sight in an infant. If an infant without sight is brought up in a normal family atmosphere, among normal-sighted companions, the ordinary landmarks of infant progress are reached at the usual time. A long-term survey and follow-up has shown that of all the patients seen in one surgeon's outpatient clinic at Moorfields Eye Hospital in City Road in a year, only about 1 child is proved to be blind from birth.

Dr. RONALD MAC KEITH emphasised that the sensory capacity in an infant was judged largely by what an infant did, and behaviour might be affected and blindness mimicked by any weak link in the chain—sensation, perception, thinking and feeling, motor activity. Examination of the degree of partial blindness in infants might be complicated by associated intellectual handicap. Of older blind children 25% were ineducable; and perhaps another 25% were educationally subnormal. The doll's-eye phenomenon, manifest in the first week of life, is demonstrated by holding up an infant and gently turning it round one way, when the eyes will turn away from the direction of motion. In later weeks the eyes turn towards the direction of motion. If an older child has the early eye sign, then this may be regarded as a sign of poor vision.

The emotional disturbance shown by parents of blind children was preventable if proper steps were taken from the first suspicion of blindness. There is then the chance of the child developing a good personality by growing in a warm family atmosphere. It is important for a baby to be able to keep in touch with its parent visually and aurally; and if there is visual defect then the aural route is more important and the mother must talk and make noises for the infant to know of her presence.

Management of Hormonal Exophthalmos

Dr. JOHN LISTER recalled that the classical triad of thyrotoxicosis, goitre, and exophthalmos gave an inadequate picture of the very varied symptomatology of this condition—a complexity to which the great number of possible labels bore witness, his own preference being for " hyperophthalmopathic Graves' disease ". And this complexity seemed no nearer resolution while the precise ætiology and pathological physiology remained obscure and its treatment correspondingly unsatisfactory. In the management of such cases of hormonal exophthalmos the degree of thyroid function should first be regulated; if it was excessive, antithyroid therapy should be given, but this had the risk of enhancing the exophthalmos, so that reversible measures (antithyroid drugs) were preferable to an irrevocable thyroidectomy when the danger signs of lid swelling, chemosis, or ophthalmoplegia were in any way apparent. In euthyroid cases, the anterior pituitary could be depressed by thyroid hormones, œstrogens or steroids, or by irradiation of the pituitary. In the hypothyroid cases, thyroid extract should always be given. Where intra-orbital tension became dangerously high, diuretics could be given, but these had been of little benefit; and surgical decompression might be necessary.

Mr. H. B. STALLARD discussed the surgical measures that might be required to relieve a more severe exophthalmos, and emphasised the importance of a timely tarsorrhaphy in order to protect the cornea, aided if necessary by an orbital fasciotomy and lateral canthal ligament division. Where a tarsorrhaphy was impossible or had failed, a large hood-shaped conjunctival flap might yet protect the cornea. Orbital decompression was necessary when the optic nerve became too stretched or showed papillœdema—either by orbital fasciotomy and excision of herniating œdematous fat or by a lateral orbitotomy.

Mr. MURRAY FALCONER emphasised that this disease was usually self-limiting so that a natural remission had often given spurious credit to the various forms of therapy. When corneal ulceration was imminent, he preferred a Naffziger decompression; and even if the exophthalmos progressed postoperatively, the orbital contents could then be more easily displaced backwards so that a tarsorrhaphy had the greater chances of success. Occasionally these patients died from myocardial infarction, which seemed to have some relation, as yet unexplained, to the hormonal exophthalmos.

Mr. T. KEITH LYLE discussed the surgical treatment of the diplopia which may accrue. He first recalled how easily such monocular cases were misdiagnosed; 3 out of his 32 patients had been labelled intra-orbital tumour, 2 suffering a surgical exploration, before a correct diagnosis was reached. An operation on the extraocular muscles to correct the secondary squint should be deferred until the condition was static. In his cases an average of four years had elapsed before operation. The actual squint operations followed the usual pattern, but it was possible to operate on the contralateral antagonist or synergist only if the limitation of movement was mild, otherwise the muscles of the more ophthalmoplegic eye would have to be resected or recessed; and it was most important to avoid any residual limitation in adduction or depression. Mr. Lyle also described a number of his cases showing a very inconstant visual field loss, presumably due to pressure on or œdematous infiltration of the optic nerve, and sometimes associated with the papillœdema. A spontaneous recovery followed.

Some Other Subjects

Discussing the advantages and disadvantages of the corneal microlens in comparison to the moulded contact lens, Mr. H. TREISSMAN said that the new problems presented by the microlens were, if anything, greater than the difficulties normally experienced with the moulded contact lens.

Dr. C. R. S. JACKSON considered the familiar complaint of asthenopia or " eye-strain ". He assessed its age-distribution and the problems of diagnosis, with particular stress on the misuse of spectacles for fine close work.

Miss AUDREY MITCHELL discussed the purposeful use of colour, starting with its historical use and symbolic value, its availability and recent technical achievements. She described the functional use of colour in various institutions and environments.

Dr. H. O. LITTLE said that the treatment of dendritic corneal ulcers required the frequent intravenous injection of vitamins, which had become deficient because of poor assimilation following psychological stress.

Dr. PAUL WEINSTEIN had noted how anisokoria often followed the dark-room test, which seemed to show that the optico-vegetative and the photo-vasopressor reflexes had importance in the pathogenesis of glaucoma.

Mr. E. S. PERKINS discussed those cases of open-angle glaucoma in the younger age-groups, which showed heavy pigment deposits on the trabeculæ, possibly thus obstructing the outflow.

Prof. B. ROSENGREN described an instrument he had devised for indenting the sclera by a silver sphere, in order to bring choroid and retina into apposition during the surgical treatment of retinal detachment.

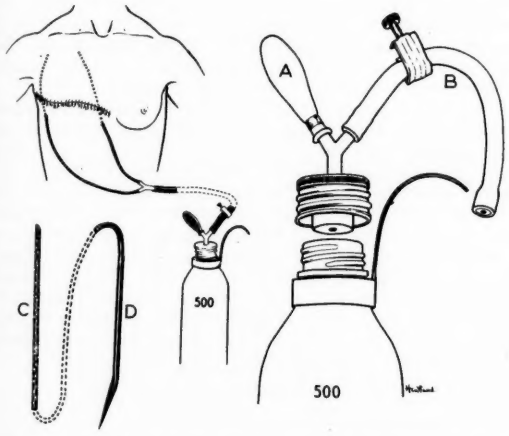
Dr. I. ISAKSSON discussed congenital blepharoptosis in the light of his anatomical dissections and electromyographic studies, which suggested that there were degenerative changes of the type seen in primary muscular dystrophy.

New Inventions

A SIMPLE SUCTION BOTTLE

OBLITERATION of the dead space in surgery by means of negative pressure has become accepted practice. The methods of applying this negative pressure often have the disadvantages of expense, immobility, and complexity. Redon [1] described a method of providing continuous negative pressure by means of a suction bottle, previously exhausted on a powerful electric or Sprengel water pump. This has the advantages of being portable, silent, cheap, and easily sterilised. I have been using a simplified version of this bottle which has proved very effective.

The apparatus consists of a National Blood-transfusion bottle sealed with a rubber bung through which passes a



plastic Y tube (see figure). To one limb of the Y tube is fixed a rubber teat (A) of the kind which is used on a medicine dropper. To the other limb is attached a length of pressure-tubing (B), which carries a screw clip. When negative pressure is applied to the bottle, the rubber teat will collapse; when the pressure within the bottle approaches that of the atmosphere, the elasticity of the rubber will cause the teat to re-expand. The critical pressure is 5 cm. Hg. The teat therefore acts as a simple indicator of negative pressure within the bottle.

Method of Use

Airtight closure of the skin is effected with sutures or clips and 'Nobecutane'. Small-bore drainage tubes (no. 4 polyethylene 2 mm. internal diameter 1 mm. wall) are brought out at a separate site. The end of the drainage tube placed within the tissues has a series of lateral holes (C) after the manner of a Carrel-Dakin tube. The tubes are carried through the skin on a carpet bodkin of the same external diameter (D). The blunt end of the bodkin is ground to the same diameter as the inside of the tube and has a series of serrations so that the polyethylene tube once fixed on the end does not easily become displaced. This method of perforation of the skin is simple and assures that the hole exactly fits the diameter of the tube. The polyethylene tube is cut off from the bodkin and pushed into the end of the pressure-tubing issuing from the suction bottle, and the screw clip is released. Sterilised bottles are evacuated to 60 cm. Hg through side-arm B before use, and can be stored in this condition for a week or more. Suction will normally be maintained until seepage from the wound has ceased; this in practice will be in 48 to 72 hours. When the teat (A) re-expands, demonstrating no negative pressure in the bottle, the bottle should be changed. More than one drainage tube can be connected, by means of a Y tube, to a single bottle, as in the figure.

I have found this method effective in closing the dead space in all situations where large areas of skin are raised, or where large tumours are removed. It is of particular use in thyroidectomies, radical mastectomies, parotidectomies, block dissection of the groin and neck, and amputations.

The prototype was manufactured for me by A. L. Hawkins & Co. Ltd., 15, New Cavendish Street, London, W.1.

Middlesex Hospital, London, W.1

K. LLOYD WILLIAMS
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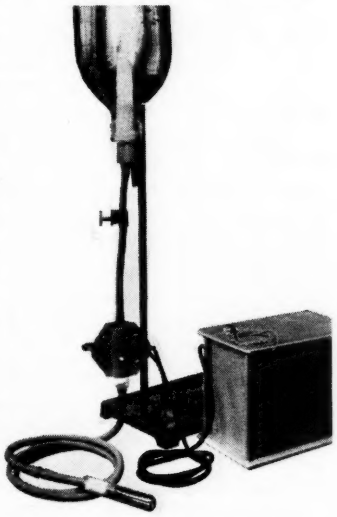
1. Redon, H. *Revue du Practicien*, 1956, **6**, 2205.

A TRANSISTORISED DRIP INDICATOR

THE increasing use of drip therapy for intravenous, subcutaneous, and intragastric purposes, leads to a greater strain on the nurses responsible for checking each drip chamber. This indicator gives a simple and reliable remote indication of drip-rates, whether the liquid is opalescent or clear.

As each drop leaves the drip tube a small lamp attached to the giving set will flash. The advantage of the device is that it fails "safe", as any fault will cause the indicator lamp to stop flashing and so will draw immediate attention to the failure.

The indicator is made up of three units: (1) the combined amplifier and battery box, which can be placed at the base of or near the giving-set stand; (2) the drip detector, which is a small plastic moulding, clipped to the drip chamber of the giving set; and (3) the indicator lamp, which can be placed in any convenient position. The drip detector consists of a flash-lamp bulb and a phototransistor so arranged that the beam of light falling on the phototransistor from the lamp is interrupted by the falling drop. The pulse signal from the phototransistor is fed into a transistor amplifier, the output from which is used to light an indicator lamp which flashes each time the light beam is interrupted.



The light beam is considerably reduced in intensity by opalescent liquids; in clear liquids a sufficient change in light intensity for correct operation is brought about by refraction and internal reflection. The length of the output pulse, and hence the duration of the flash from the indicator, is variable and is adjusted by a rheostat on the amplifier box.

The unit contains no moving contacts or relays, and the only maintenance is the replacement of batteries and lamps when necessary. A mains-driven power unit can be fitted in place of the battery. A separate unit can be plugged into the amplifier box to record the rate of drip over one minute, and the total number of drips given.

I acknowledge with thanks the help given to me by G. R. Burgess & Co. Ltd., Southall, in the development of this useful device, and to Mr. H. G. Jones and Mr. D. W. Allen for their technical assistance. The device is obtainable from this firm, but the price has not yet been fixed as a prototype only has been produced. The cost should not be high once the indicator can be produced in quantity.

London, W.1

R. DANBURY
M.B. Lond., D.PHYS.MED.

Reviews of Books

Orthopædics

Principles and Their Application. SAMUEL L. TUREK, M.D., attending orthopedic surgeon, Weiss Memorial Hospital; associate attending orthopedic surgeon, Mount Sinai Hospital. London: Pitman Medical Publishing Co. 1959. Pp. 906. 160*s*.

Dr. Turek's book is probably the largest and most comprehensive single-volume work on orthopædics yet published: certainly it is one of the most attractive and easily read. Its general plan conforms to that of many similar works. There are six introductory chapters on the normal structure and physiology of the skeleton and the connective tissues, and two principal sections which deal with orthopædic diseases on an ætiological and a regional basis. Three features, however, set the book apart. One is the large number of illustrations, including over 50 excellent coloured plates: another is the detailed way in which each condition is discussed, with reference to a brief *and* very international bibliography. The third is the inclusion of many "medical" topics—such as peripheral vascular disease and the muscle dystrophies—about which every surgeon needs information from time to time. This book contains much valuable advice on these disorders, which are not considered at all in many long-established orthopædic texts.

It is easy to believe that Dr. Turek has, as the foreword states, devoted many years of his life to the preparation of this book; and the product of his labours will be read and admired for a long time to come.

In Place of Parents

GORDON TRASLER, PH.D., lecturer in social psychology, University of Southampton. London: Routledge & Kegan Paul. 1960. Pp. 248. 25*s*.

Dr. Trasler's book describes an investigation of all the cases of foster care in one local authority's area during a three-year period. His study sample consisted of children who had known at least one failure in placement in a foster home, and they were compared with children whose placement had succeeded. This detailed study of a limited number of cases not only revealed some of the psychological processes involved but also showed vividly what success or failure can mean to the individual children and parents. As the author points out, the observation of children and parents in these somewhat unusual situations can give insight not only into the various difficulties of the people concerned, including the responsible and delicate role of the case-worker, but also into some emotional problems of ordinary parents and children. Although he emphasises that techniques of home-finding have progressed considerably in the past two decades, so far comparatively little work has been published on this subject in this country. Many of the observations in this book suggest further fields of study, and will surely be of great value to all students and social workers. Dr. Trasler confirms that the greatest need of any child is some enduring and affectionate personal relationship, a difficult thing to achieve in even the most successful institution. Foster care is one answer, and this book will contribute to an understanding of the complications, challenges, and rewards in the whole business of finding and keeping happy foster homes.

Cancer of the Breast

Editor: WILLARD H. PARSONS, M.D., F.A.C.S., director of surgery, Vicksburg Hospital. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 232. 60*s*.

Dr. Willard Parsons and his eleven collaborators set out to provide a concise discussion of the more important aspects of breast cancer, particularly from the clinician's viewpoint. They have clearly succeeded in this beautifully produced and illustrated book. Their views on the surgery of breast cancer do not differ widely from those of most surgeons in this country, but the chapter on the role of the radiologist expresses doubt on the value of all postoperative irradiation—after either radical or simple mastectomy—a view which would not command general acceptance here.

Foote's chapter on pathology is admirable, though one could have wished for more discussion on pre-malignant proliferative changes and sclerosing adenosis. Marshall's contribution on the technique of radical mastectomy is also excellent, and Urban adds a very fair and balanced account of his super-radical operation and its results to date. It is perhaps the fault of his subject that the editor, in summing up, cannot come out with more definite advice on what to do, despite his undertones in favour of radical mastectomy. For a short, readable, and conservative summary of the position, this book is commended.

An Atlas of Dental and Oral Radiology

SYDNEY BLACKMAN, M.R.C.S., D.M.R.E., consultant radiologist, Royal Dental Hospital of London. Bristol: John Wright & Sons. 1959. Pp. 384. 84*s*.

HERE is a fine collection of 816 reproductions of dental and extra-oral X-ray films covering a wide range of subjects. The standard of reproduction is mostly very good, particularly the enlarged apical films, but reproduction of the extra-oral films is more variable. Presentation of the films is usually correct—as if viewing the patient directly—but there are a few inconsistencies, particularly with lower occlusal films.

The atlas is arranged with introductory discussions to the sections and to some subsections, and the range of headings is wide and generally good. The discussions tend to be rather wordy and are not always very informative—for example, the extended one on caries. Terminology is sometimes loose, as "the body of the ascending ramus" in the caption to fig. 52, and the use of varied terms such as "dento-alveolar abscess", "apical abscess", "rarefying destructive osteitis", and "periapical granuloma" is likely to be confusing. These are used for what is essentially the same lesion but without drawing any distinction between them or showing in what way they may differ. On p. 24 it is stated that "the condyles of the mandible are still immature at 6 months of age": surely they are still immature at 6 years of age. Figs. 59 and 63 in the normal section, of a boy at $3^1/_2$ and at 7 years, show the severe reduction in pulp space of all the teeth that occurs in the condition congenital opalescent dentine—as is pointed out later in the appropriate section. Some points are very well made, such as the diagnosis of neurofibroma and the series of films showing pulp calcification. There are no references to the literature.

The critical reader will find many helpful illustrations of wide variety, but occasional interpretations could be misleading to the uninformed.

Peaceful Uses of Atomic Energy (*Proceedings of the Second United Nations International Conference.* Vol. 22. *Biological Effects of Radiation.* Geneva: United Nations. 1959. Pp. 552. 104*s*.).—The proceedings of this conference are published in 33 volumes. This one covers the biological effects of radiation, but does not deal with health and safety or uses of isotopes as research tools. There are 90 papers representing new original work and reviews from most of the larger radiobiological laboratories of the world. Of particular interest is the scope of the 19 papers translated from Russian, and it is a pity that in these papers it has not been possible to give addresses of the authors (in contrast to the papers in other languages). The work quoted is sometimes not given in sufficient detail to convince readers that the phenomena were always properly controlled. The opening review by A. V. Lebedinsky admirably presents the main advances achieved and emphasises the problems still outstanding. On p. 7 he cites G. J. Neary and H. J. Evans as having shown that "The number of primary injuries is reduced in the presence of oxygen" while the authors clearly state the opposite (p. 306): "The oxygen effect can be interpreted as an increase in the number of primary breaks . . ." Although this volume is clearly valuable it raises the wider question of the economic wisdom of publishing the results of giant conferences. The publication of these volumes has been a great technical feat, and the purchase price probably represents only a fraction of the true cost.

THE LANCET

LONDON 23 APRIL 1960

Thrombophlebitis following Intravenous Infusion

THROMBOPHLEBITIS has long been known to follow intravenous infusion. The possible causes are several. First, the needle may damage the venous endothelium; and accordingly for long-continued infusions polyethylene catheters have been recommended. Secondly, the infusion fluid may be the cause. 5% glucose solution is regarded by many as relatively hazardous because of its low pH, though BOLTON CARTER et al.[1] found that the incidence of thrombophlebitis was unchanged by using buffered glucose at a pH approximating to that of blood. A third factor is the duration of the infusion. BOLTON CARTER [2] found that the incidence of thrombophlebitis increased considerably when infusion was continued for more than eight hours. A further factor is the nature of the tubing used in the giving set. Until quite recently this consisted of rubber with glass and metal parts. HANDFIELD-JONES and LEWIS [3] established that the incidence of thrombophlebitis was influenced by the kind of rubber tubing from which the giving-set was made; the incidence was lowest with pure latex tubing. Various reports suggest that when infusions are given through the National Blood Transfusion Service rubber set and continued for more than twelve hours, the incidence of thrombophlebitis may be greater than 50%.

In the manufacture of rubber tubing, various compounds are added to promote vulcanisation; and the differences in the incidence of thrombophlebitis associated with different samples of rubber tubing, together with the close correlation between this incidence and the duration of infusion, suggests that a substance giving rise to thrombophlebitis is leached from the rubber tubing through which the fluid passes. The use of plastics as an alternative for intravenous infusion sets is not entirely free from danger; for plasticisers and stabilisers added in order to obtain plastic in a suitable form for the manufacture of tubing may be harmful. A Medical Research Council trial [4] in which a plastic set and the standard red-rubber set were compared confirmed that the duration of the infusion was important: where the infusion lasted less than twelve hours the incidence of thrombophlebitis was nil, but beyond this period it increased appreciably for each set with the duration of infusion. With infusions lasting longer than twelve hours, the incidence of thrombophlebitis with the plastic giving-set was only half that with the red-rubber set; nevertheless thrombophlebitis developed in as many as 18% of cases when plastic tubing was used.

The toxicity of red-rubber tubing has been assessed by testing its ability to inhibit the growth of *Streptococcus pyogenes*. The possible danger of plastics in surgery can be evaluated by implantation into animals; but this is not an effective method of determining early toxic activity. CRUICKSHANK et al.[5] have examined the effects of rubber and plastic on the growth of tissue-cultures of chick embryo, the oxygen uptake of skin tissue-cultures, and the growth of *Str. pyogenes*. It was found that materials which inhibited growth of *Str. pyogenes* were also toxic to tissue-cultures, but that some materials which were toxic to tissue-cultures did not inhibit bacterial growth; the latter is a less satisfactory test. Tests of the relative toxicity of materials by the two tissue-culture methods were in agreement. The relative toxicity of the materials, revealed by these tests, could be correlated with the differences in the incidence of thrombophlebitis after intravenous infusions administered through giving-sets assembled from the materials tested; and CRUICKSHANK et al. conclude that "the toxicity revealed by these tests is of clinical importance, and that tissue culture toxicity tests will prove to be of value in selecting rubber and plastics for clinical purposes".

Plastics are used not only for rubber tubing but also for bags in which blood is stored for transfusion. In the U.S.A. each batch of plastic bags is tested by estimating the survival of cells in blood stored in these bags for twenty-one days at 5°C—the proportion surviving must be greater than 70%. A laboratory test which could save the need for such work would clearly be valuable. But the present tissue-culture tests are technically difficult; and we hope that CRUICKSHANK and his colleagues will continue their investigations with the aim of adapting these tests for routine use.

Krebs Cycle

ENERGY required by the body to perform work can be derived from protein, fat, or carbohydrate; but normally carbohydrate is preferentially burned as the main energy source (although fatty acids can also be similarly oxidised) while protein and fat are used for body building and storage respectively. Food required for energy is oxidised in a series of steps by which hydrogen is transferred via a hydrogen acceptor (diphosphopyridine nucleotide [D.P.N.] or triphosphopyridine nucleotide [T.P.N.]) to cytochrome under the catalytic influence of a flavoprotein. The ferric iron of cytochrome is reduced to the ferrous state before another

1. Bolton Carter, J. F., Milne, E. H., Whittet, T. D. *Lancet*, 1952, ii, 660.
2. Bolton Carter, J. F. *ibid.* 1951, ii, 20.
3. Handfield-Jones, R. P. C., Lewis, H. B. M. *ibid.* 1952, i, 585.
4. Medical Research Council Subcommittee, *ibid.* 1957, i, 595.
5. Cruickshank, C. N. D., Hooper, C., Lewis, H. B. M., MacDougall, J. D. B. *J. clin. Path.* 1960, **13**, 42.

iron-containing enzyme, cytochrome-C oxidase, transfers the hydrogen to oxygen and the process of oxidation is complete. During this series of reactions energy is captured and stored as high-energy phosphate bonds in the form of adenosine triphosphate (A.T.P.). It is now believed that three or possibly four such bonds are generated during the transfer of two hydrogen atoms to oxygen.[1]

Detailed study of the steps whereby the body breaks down carbohydrate has led to the identification of the points at which energy-rich phosphate bonds are formed. Glucose, derived either from the blood or from tissue stores of glycogen, is phosphorylated and then either broken down anaerobically by the classical Embden-Meyerhof pathway to pyruvate or oxidised to phosphogluconic acid and then to the pentose, ribose-5-phosphate. The importance of this last reaction may be in the supply of building blocks for the synthesis of ribose nucleic acid, but evidence suggests that the pentose may also be broken down to a triose which can itself give rise to pyruvate.[2] The proportion of glucose burned in either of these pathways is not known and probably varies in different tissues and at different times. During anaerobic glycolysis glucose gives rise to two molecules of pyruvic acid and four energy-rich bonds are formed; but as one such bond has previously been required for phosphorylation there is a net gain of three molecules of A.T.P.

When anaerobic conditions exist in the tissues—for instance, in active muscle—pyruvate can be reduced to lactic acid, the final stable product of glycolysis; but the energy yield per mole of glucose is poor compared with that obtained by the complete oxidation of pyruvate to carbon dioxide and water via the tricarboxylic-acid or Krebs cycle.[3] Before it can enter the cycle pyruvate must undergo a further series of reactions which convert it to "active acetate", which then condenses with oxaloacetate to form citrate [3 4]; two carbon fragments of fatty-acid oxidation also employ this common pathway.

These reactions might be described as the Achilles heel of the cycle, for they represent the principal point at which a metabolic block may occur. At present at least five co-factors are believed to be necessary to complete the decarboxylation of pyruvic acid—thiamine as thiamine pyrophosphate (T.P.P.), reduced coenzyme A (Co-A-S.H.), D.P.N., magnesium ions, and lipoic acid (6:8 dithio-octanoic acid). REED [5] has suggested that the reactions may take place in the following sequence: pyruvic acid combines with thiamine pyrophosphate to form acetyl T.P.P.; this in turn reacts with lipoic acid to yield acetyl lipoic acid, which can then react with reduced coenzyme A to form acetyl Co-A and reduced lipoic acid; the lipoic acid then reforms its internal disulphide bridge by handing on hydrogen to D.P.N., while the acetyl Co-A is ready to transfer the acetyl group to oxaloacetic acid with which it will condense to form citric acid, the starting-point of the Krebs cycle. During this series of reactions three high-energy bonds are generated. Citric acid is a six-carbon, tricarboxylic acid which, under the influence of the enzyme aconitase, forms first cis-aconitic and then iso-citric acid, and the series of reactions then proceeds according to the steps postulated by KREBS.[4] Iso-citric acid is further oxidised by transferring two hydrogen atoms to T.P.N., oxalosuccinic acid is formed, and a further three high-energy bonds are generated. Oxalosuccinic acid loses carbon dioxide to give rise to α-ketoglutarate, a five-carbon acid the further oxidation of which may be another Achilles heel in the cycle. As an α keto acid, ketoglutarate requires the same five co-factors for its further oxidation as does pyruvate and similarly gives rise to the formation of three high-energy phosphate bonds. In addition, ketoglutarate takes part in transamination reactions with both aspartic acid and alanine and may represent the final common path whereby aminoacids enter the cycle to undergo complete oxidation; and it can act as an acceptor of ammonia and probably has a key role in the ammonia-binding mechanisms of the cell.[6] Moreover, in mammalian nervous tissue ketoglutarate enters into a shunt reaction by-passing the thiamine-dependent decarboxylation of the keto acid. After taking up ammonia to form glutamate it is converted via γ-aminobutyric acid to succinic semialdehyde and then re-enters the main cycle as succinic acid.[7] This series of reactions is vitamin-B_6-dependent, and the convulsions in pyridoxine deficiency in man and animals may be due to a biochemical lesion at this point.

From this point the ensuing steps of the cycle may be summarised as follows. Succinyl Co-A, derived from ketoglutarate, gives rise to the four-carbon compound, succinic acid, with the formation of one high-energy bond. The succinic acid is then acted on by succinic dehydrogenase to form fumaric acid and two further high-energy bonds. Fumarate in turn yields malate which, to complete the cycle, gives up a further two hydrogen atoms to form oxaloacetic acid together with a final three high-energy bonds. Thus each molecule of pyruvate is responsible for the generation of fifteen molecules of A.T.P. or thirty such bonds for each molecule of glucose. This is much more efficient than the simple glycolytic process, and any lesion of this complicated and highly efficient system of energy capture may be disastrous to the organ or organism concerned. Moreover, not only carbohydrate but also protein and fat metabolism may be involved. It has already been shown how aminoacids can enter the cycle after transamination; and fatty acids, once they have undergone β-oxidation to acetoacetate, can give rise to acetyl Co-A which then enters the cycle by the series of reactions already described.

The elucidation of the various steps involved in glucose oxidation has given less help to the clinician

1. Strickland, K. P. *Guy's Hosp. Rep.* 1956, **105**, 108.
2. Racher, E. *Advanc. Enzymol.* 1954, **15**, 141.
3. Krebs, A. H., Johnson, W. A. *Enzymologia*, 1937, **4**, 148.
4. Krebs, A. H. *Advanc. Enzymol.* 1943, **3**, 191.
5. Reed, L. J. *ibid.* 1957, **18**, 319.
6. Weil Malherbe, H. *Physiol. Rev.* 1950, **30**, 549.
7. Tower, D. B. *Int. Congr. Biochem.* 1958; symposium 111.

than might have been hoped. Almost nothing is known of naturally occurring disorders of the Krebs cycle, possibly because breakdown of such an essential energy source would be disastrous to the body. To Sir RUDOLPH PETERS we owe the concept of the " biochemical lesion ", and appropriately enough it was his school at Oxford [8] that localised the first block affecting what subsequently became known as the Krebs cycle. This work of the Oxford school showed both in vitro and in vivo that pyruvate and lactate accumulated in the blood and brains of pigeons on a thiamine-deficient diet and that this metabolic defect could be reversed by restoring the vitamin to the diet. A similar block in glucose oxidation was later demonstrated in man, also when thiamine was deficient, giving rise either to beriberi [9] or Wernicke's encephalopathy.[10] Thiamine deficiency might also be expected to interfere with the oxidative decarboxylation of ketoglutarate at a later stage in the cycle, but there is no evidence that this takes place either in vitro or in vivo. Tervalent metals will also block the entry of pyruvate into the cycle, and again we owe our knowledge of this to the Oxford school of biochemists.[11] Arsenite, by combining with the dithiol lipoic acid, inhibits the formation of acetyl Co-A—a reaction which can be reversed by 1:2 dimercaptopropanol (dimercaprol, BAL), which transfers the arsenic from the six-sided to a more stable five-sided ring, leaving the lipoic acid free to carry out the transfer of acetyl groups from thiamine to coenzyme A.

The action of fluoroacetic acid in interrupting the cycle is hardly of clinical interest (although it has been used as a poison by witch doctors to produce the fatal illness " broke back " [12 13]; but it is of considerable theoretical importance, for it gave rise to the theory of " lethal synthesis "—yet another concept we owe to PETERS. Fluoroacetic acid enters the cycle in the same way as " active acetate " and condenses with oxaloacetic acid to form fluorocitric acid; this blocks the enzyme, aconitase, so that citric acid itself cannot be converted to cis-aconitate, the cycle is inhibited, and citric acid accumulates in the tissues.[14] The hypothesis that the ensuing convulsions result either from interruption of the energy supplies of the cell or the deionisation of calcium following the accumulation of citric acid has been challenged by BENITEZ et al.,[15] who demonstrated that in fluoroacetate poisoning a rise in the brain concentration of ammonia preceded the rise in fluorocitrate and exceeded it on a molar basis, reaching its peak at sixty minutes, just before the onset of epileptic seizures. These workers believed that the fits were due not so much to interference with the Krebs cycle as to the accumulation of ammonia. Whichever is the correct interpretation, the action of fluoroacetate in inhibiting aconitase and causing the accumulation of citrate supports current theories on the mechanism of pyruvate incorporation into the cycle. No metabolic lesions are known to affect the steps whereby cis-aconitate is converted to ketoglutarate, but the decarboxylation of this keto-acid is inhibited by arsenite and presumably by other factors which also interfere with pyruvate oxidation. Furthermore ketoglutarate may be drained from the cycle at this point by excess ammonia in the tissues [16]; and BESSMAN and BESSMAN [17] have suggested that the conversion of ketoglutarate first to glutamate and then to glutamine in the presence of excess ammonia is the fundamental lesion underlying hepatic coma. Whether this reaction takes place in vivo has to be proved, but the brain contains transaminases which can transfer unwanted amino groups to other keto acids with the regeneration of ketoglutarate. Whether shortage of ketaglutarate can act as a rate-limiting step in the cycle also remains to be proved; but blood levels of ketoglutarate have not been observed to fall in the presence of raised values for blood-ammonia. Nevertheless, this hypothesis is of great theoretical interest, and if proved correct it will have provided the first example of a naturally occurring block at this stage of carbohydrate oxidation.

Once ketoglutarate has been converted to succinyl Co-A the reactions taking it on to oxaloacetate can be interrupted only by the selective inhibition in vitro of succinic dehydrogenase by malonate (other less specific enzyme poisons such as fluoride can hardly be considered here). The final step in the cycle—the condensation of oxaloacetate with acetyl Co-A—is probably rate-limiting and must itself depend on the availability of oxaloacetate for completion.

No mention has been made of less well-defined disorders of carbohydrate oxidation, such as the accumulation of lactate and pyruvate in the blood of patients with Cushing's syndrome or on steroid therapy,[18] or of the low levels of tricarboxylic acids in the tissues of diabetic animals; for these abnormalities are believed to be due to a failure of pyruvate oxidation and not to inhibition of the cycle itself.[19] Other conditions in which abnormalities of carbohydrate oxidation have been reported include subacute combined degeneration of the cord, disseminated sclerosis, and schizophrenia.[20] The locus of the metabolic lesion in these conditions has yet to be identified.

As yet no genetically determined lesion of the cycle has been reported, but with the increasing entry of biochemical techniques into clinical investigation it is probably only a matter of time before such a condition is discovered. If the theory of one gene one enzyme is accepted there should be an inherited disorder for each step in the cycle, unless such a fundamental interruption of the energy sources of the cell is incompatible with life.

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9. Platt, R. A., Lu, G. D. *Biochem. J.* 1939, **33**, 1525.
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13. Peters, R. A. *Proc. roy. Soc.* B. 1952, **139**, 143.
14. Peters, R. A. *Bull. Johns Hopk. Hosp.* 1955, **97**, 21.
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17. Bessman, S. P., Bessman, A. N. *J. clin. Invest.* 1955, **34**, 622.
18. Henneman, D. H., Bunker, J. P. *Amer. J. Med.* 1957, **23**, 34.
19. Frohman, C. E., Orton, J. M., Smith, A. H. *J. biol. Chem.* 1951, **193**, 803.
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Annotations

TREATMENT OF SALICYLATE POISONING

THE complex actions of salicylate in poisonous amounts are gradually becoming more clearly understood.[1] Respiratory alkalosis is probably the first change in most, if not all, cases; but this is followed by metabolic acidosis the causes of which are the acidity of aspirin, interference with carbohydrate metabolism, and renal dysfunction. Metabolic acidosis rapidly worsens as liver glycogen is depleted by starvation and increased metabolism. Besides the problems of alkalosis and acidosis there are those of dehydration, hyperthermia, and potassium loss. Formerly the treatment of severe poisoning was rather unsatisfactory owing to ignorance of these disturbances.

Gastric lavage with water is urgently necessary. (Prof. J. M. Webster [2] stated emphatically in court recently that the prevalent idea that gastric washouts are unnecessary is quite wrong.) Aspirin and methyl salicylate may remain in the stomach many hours before absorption, and it is hardly ever too late to try to remove them. Continuous washing of the stomach is perhaps advisable, as salicylate may possibly be excreted into the stomach or be regurgitated from the small intestine during vomiting. Enemas and cathartics have been recommended in the past—and not without good reason, if the patient is fit enough, for salicylate is probably present in the intestine for some hours and may be eliminated by these measures.

The treatment of the disturbance of acid-base balance should be regulated by blood or urine pH changes. Plasma-carbon-dioxide levels are unreliable because they may be lowered either by respiratory alkalosis or by metabolic acidosis. In the alkalotic stage alkali should be avoided. In most severe cases the patient has a metabolic acidosis by the time he reaches hospital, and this can be well treated with intravenous sodium lactate, or with oral sodium bicarbonate which also increases urinary excretion of salicylate. Overloading with fluid should be avoided, particularly if there are signs of oliguria.[3] Serum sodium and potassium levels should be estimated in order to avoid or to correct hypokalæmia or hypernatræmia. Glucose, given alone or with lactate, is necessary to restore depleted carbohydrate. Hyperpyrexia is prevented or treated by exposure and cold applications. It is wise to give a vitamin-K analogue in order to avert hæmorrhage, and other vitamin supplements can do no harm. Antibiotics, assisted respiration, and physiotherapy are needed in some cases.

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Annotations

TREATMENT OF SALICYLATE POISONING

THE complex actions of salicylate in poisonous amounts are gradually becoming more clearly understood.[1] Respiratory alkalosis is probably the first change in most, if not all, cases; but this is followed by metabolic acidosis the causes of which are the acidity of aspirin, interference with carbohydrate metabolism, and renal dysfunction. Metabolic acidosis rapidly worsens as liver glycogen is depleted by starvation and increased metabolism. Besides the problems of alkalosis and acidosis there are those of dehydration, hyperthermia, and potassium loss. Formerly the treatment of severe poisoning was rather unsatisfactory owing to ignorance of these disturbances.

Gastric lavage with water is urgently necessary. (Prof. J. M. Webster [2] stated emphatically in court recently that the prevalent idea that gastric washouts are unnecessary is quite wrong.) Aspirin and methyl salicylate may remain in the stomach many hours before absorption, and it is hardly ever too late to try to remove them. Continuous washing of the stomach is perhaps advisable, as salicylate may possibly be excreted into the stomach or be regurgitated from the small intestine during vomiting. Enemas and cathartics have been recommended in the past—and not without good reason, if the patient is fit enough, for salicylate is probably present in the intestine for some hours and may be eliminated by these measures.

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that in all the patients the disorder was derived from a single ancestral couple about four hundred years ago. Because of the genetic unity of this series, the conclusions drawn from it may not all be applicable to other patients with essential tremor, in whom it may possibly be due to a different mutation; but, their series being unselected, Sjögren and Larsson have been able to make a most valuable assessment of the variability and course of at least one form of this condition.

FOOD-POISONING

MEDICINE is international; but medical education, the conditions of practice, and even the fundamental emphases of pathology are not. Hence there are disadvantages as well as advantages in the kind of international report which the World Health Organisation so often produces. The experts assemble for a few days or weeks; they work hard to discover the highest common factor in their ideas; they conceal their very obvious differences; and they have to produce a statement. Not unnaturally the result is sometimes a minim of facts diluted in an ocean of truisms. The report of the European Technical Conference on Food-borne Infections and Intoxications,[1] for example, gives us 16 pages on the classification of food-poisoning, its detection and notification, and some measures for its control; but there is nothing new in it, and collaboration has lowered instead of raising the level on which these authorities write. Incidentally, it does not mention one of the most pressing dangers in the international trade in food—the use of organic phosphate insecticides on fruit and vegetables.

Meat and eggs from continental Europe have played a small part in causing food-poisoning in Great Britain and have introduced a few species of salmonella hitherto unknown here. Similar introductions have no doubt occurred in other countries, but of this we have no evidence. Are we receiving the overflow from some great epidemic—as we do of foot-and-mouth disease or Colorado beetles—or is this an example of a slow and continuous spread of infectious agents which do not regard political boundaries?

The answer may be derived from the better reporting of food-poisoning, which, as this report hints, might be more complete and more accurate everywhere. In England we are probably better served than in most countries. Our medical officers of health are responsible for relatively small areas; our laboratory service is adequate; and no-one lacks medical attention because of his poverty. Most outbreaks of food-poisoning in institutions and communities are known, and they are often investigated thoroughly. But the reporting of individual and familial infections (which may be just as important to the epidemiologist) is less satisfactory, for two reasons: many adults do not seek medical advice for an ailment which does not send them to bed and which upsets their lives less than a severe cold; and many practitioners do not report a disease which appears to affect only one or two and which (in most instances) cures itself. If we with all our manifest advantages fail in reporting all cases of food-poisoning, we cannot expect any better from poorer countries where doctors and laboratories are few, where such diseases as enteric fever are still endemic, and which have tougher populations that seek medical attention only in dire necessity. In these less fortunate countries a good deal has been learnt about some other diseases by the intensive study of a sample of the population. The report does not mention these methods, which might tell us more about the prevalence and origin of food-poisoning than the sporadic and incomplete returns from a whole nation.

Despite tariffs and quotas the international trade in food within Europe is considerable. Dr. Hobbs and her colleagues have shown that the bacteriological examination of imported food can reveal dangers which had not been suspected.[2] Yet it may be easier to sample imported than home-produced foodstuffs. We may see the day when the sanitarian replaces the customs officer at the frontier (or maybe the frontier itself will disappear), and meanwhile there is much to be said for an international agreement for the sampling of imported foods and the tracing of infectious agents to their origin. On the whole, however, food-poisoning is not a subject which encourages useful international action. The need for international measures may be clear to the experts, but it is not yet so obvious to the many other parties interested—the veterinarians, agricultural, transport, wholesale and retail trades, and the consumer. The technical problems are the least difficult to solve: the hardest in all countries is to persuade the public that some action is necessary.

STATUTORY SANCTIONS?

IN preparation for its move from Pall Mall East to Regent's Park the Royal College of Physicians has presented a private Bill to Parliament [3] to modify and modernise some of its ancient rights. It seeks approval to hold meetings "anywhere in England", instead of, as at present, only in Westminster or the City; it seeks to be allowed to hold land of an annual value exceeding the present limitation of £1000; and it seeks formal authorisation for its name, which, though used in the Medical Acts since 1858, has not appeared in many of the college's own legal documents.

At first, or indeed at second, sight the Bill does not seem controversial, and it has passed without comment or incident through the House of Lords. In the Commons, however, its progress has been blocked by a motion tabled by Dr. Barnett Stross, supported by Mr. Kenneth Robinson, Dr. Dickson Mabon, Miss Margaret Herbison, Mr. Ellis Smith, and Mrs. Harriet Slater. When the Bill was called for a second reading on April 12 Dr. Stross again objected, and the second reading has now been deferred till April 26 when it will be debated.

To *The Times* [4] the group have explained that their motive in hindering the progress of the Bill is "to get changes in the by-laws of the college so that Fellows and members will have a more effective voice in the affairs of the institution". On this subject they seem to be imperfectly informed; and even those who may sympathise with their aims will hardly condone the means they are adopting. The constitution of a learned body and its methods of conducting business are a domestic and professional matter. To attempt to intervene by exerting legislative pressure is a misuse of parliamentary procedure.

Sir ROBERT PLATT has been re-elected president of the Royal College of Physicians of London.

1. *Wld Hlth Org. tech. Rep. Ser.* 1959, no. 184.
2. Hobbs, B. C., Wilson, J. G. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 198.
3. See *Lancet*, Jan. 9, 1960, p. 119.
4. April 13, 1960.

Special Articles

HUMAN RELATIONS IN OBSTETRIC PRACTICE *

NORMAN MORRIS
M.D. Lond., F.R.C.O.G.
PROFESSOR OF OBSTETRICS AND GYNÆCOLOGY IN THE UNIVERSITY OF LONDON AT CHARING CROSS HOSPITAL MEDICAL SCHOOL, W.C.2

DURING the past twenty-five years changes in obstetric practice have reduced the physical hazard of childbirth dramatically. This achievement has tended to make us a little complacent. Indeed some people even suggest that there are few problems in obstetrics left for us to solve. But are we to measure success simply in terms of life and death? Though the physical care of the patient has advanced, I believe that many serious gaps remain, particularly in our knowledge and understanding of the patient's emotional condition in pregnancy, labour, and the puerperium.

For most women childbirth is their moment of greatest achievement and sometimes of greatest happiness. It is an immensely important emotional as well as physical event. It is a period of great intensity of feeling and reaction. The influences that a woman meets during this time may have a tremendous psychological and social significance, and in my view our present hospital system often fails miserably in its care of the patients' emotions. The joys, hopes, and wonder that the arrival of new life should bring are spoiled, and splintered into loneliness, indignity, and despair. The feeling of personal achievement is lost, drowned in a sea of inhumanity.

My own opinions and observations have lately been reinforced by a collection of extracts from several hundreds of letters sent to a weekly women's journal,† which I have been allowed to study.

ANTENATAL CARE

Antenatal Clinics

Women attend these clinics regularly, often as many as fourteen times. The clinic is usually drab and colourless, painted in bottle green, brown, or dirty cream. There are rows of uncomfortable benches. There is an atmosphere of coldness, unfriendliness, and severity more in keeping with the spirit of an income-tax office. The clinic is often very overcrowded, and at best a crude appointment system is in operation. Despite this, women often wait 1-3 hours. The interview itself is usually extremely brief, and under such conditions there is little encouragement for the patient to ask questions or relieve herself of any nagging fears or doubts. Therefore she often remains in gross ignorance of what is happening to her. The doctors and nurses also remain virtual strangers since she rarely sees the same one at each visit.

The following extracts from the letters describe experiences in antenatal clinics:

"As you entered the doctor was already reading your case-sheet, and we were on and off the examination table in two shakes . . . barely two minutes, when we had waited perhaps two hours or more. I did meet one mother, who was on her first visit only three weeks before her baby was due. She had other children who she found it difficult to leave for so long a time. There was no system of appointments."

"The nurses and doctors were very friendly at the antenatal clinic and very helpful—but—we were rather like 'sausages in a sausage machine'. I understood that there were far too many pregnant women and far too few doctors. It was rather amusing to hear the remark of a nurse on seeing one mother-to-be making her face up. She was told 'Don't bother with your face, dear, it's the other end he's interested in'."

"The midwives at the hospital all seem to have too much on their plate to bother with the odd person who wants to know 'why, where and what'. Whenever I go for treatment, it always seems as though I were being put on a conveyor belt and passing through all the different stages—water—blood—examination and out. There seems to be nothing human in them at times."

"I am not wanting to be fussed over, but I do think a friendly reception—with a smile would go a long way to make one feel more confident about the birth. . . . One's reception is so cool, and there seems to be little interest shown at hospital, with hardly an exchange of words. In fact these seem to be minimised to 'Go in, undress, lie down' (from a very tight-lipped nurse) and 'Are you feeling any kicks?' (from the gynæcologist). More often than not, I feel like giving him a few kicks myself!"

There is a myth that patients will not keep appointments. This is not true. Appointments will be kept by the patient, if the hospital shows definitely that it intends to honour these appointments on time. Doctors interviewing large numbers of women on an endless conveyor-belt system inevitably lose their sensitivity. Not long ago I heard a senior obstetrician admit that even after seeing about eight patients he began to feel dizzy. Such an arrangement is terribly fatiguing, and yet there is little evidence that much is being done to end this archaic system.

Preparatory Classes

Many hospitals encourage some form of classes for special instruction and preparation for labour, but unfortunately there is often poor liaison between the people who run the classes and the staff of the labour ward. Few obstetricians take an active part in organising and running the classes, though physiotherapists and midwives are doing excellent work despite our lack of support.

Virtually no studies have been done on the average patient's emotional response to pregnancy and labour. We know even less about the ultimate effect of experiences in childbirth on the mother's relationship with her child and family. As a result these preparation classes are very much in their infancy. But even in their present form they do enable women to approach labour with confidence and to bring it under their own control. In my view a hospital that fails to provide such classes is as negligent in an emotional sense as it would be in a physical sense if it failed to test the urine regularly during pregnancy.

Some obstetricians and midwives still doubt the value of preparation classes. They point out that preparation has no effect on the length of labour, the forceps-rate, or the cæsarean-section rate. They are obsessed by purely physical standards. How can we produce statistics to show how many women emerge from labour exalted rather than demoralised, confident rather than afraid?

* Based on a lecture given at the opening of the new obstetric unit at Charing Cross Hospital on Feb. 23; see *Lancet*, March 5, 1960, p. 556.

† The original letters are available in the offices of the journal, but I have been sent only extracts, and I do not know the name and address of any of the patients or their hospitals.

We can measure the length of labour but not the mother's sense of achievement or wellbeing.

MANAGEMENT OF LABOUR

When the patient arrives at the hospital in labour, she usually goes through a ceremonial, known as "being admitted". Before this ceremonial can begin she often has to supply "some particulars" to the porter or nurse on duty. She is then undressed, shaved, given an enema and a hot bath. Some more active centres also treat their patients to a castor-oil cocktail. These measures can prove a little unnerving, especially if they are unexpected. When this ritual is completed the patient either goes into a first-stage labour-ward or into the general ward.

In the first-stage ward, usually a large room with several beds, there are often many women in different stages of labour. To a woman in early labour it is extremely frightening to be brought into such close contact with women in the later stages of labour and who may appear distressed and upset.

The following extracts show how much sympathetic management can contribute to the patients' morale:

"Then came the hustling process into a bath, then an enema, with my mental condition indescribable! I thought all this might injure my baby and they could not be bothered to offer the one word of comfort or explanation. From 7 A.M. till noon I did not see a soul, and was told before being left on the labour bed 'Don't keep ringing the bell, we have not the time to answer you'. Eventually, my son, an eight pounder, was safely delivered, but I had been robbed of my peace of mind for many months to come. In fact, to be frank, in my youth and ignorance, I could not bear my husband near me for a long time after the baby's birth . . ."

". . . I am a young girl of twenty-one and I had my first baby a little over two months ago. I was in labour for two days and nights, and was on my own for the whole time, except for occasional heads being popped round the door, and when my husband could come. I had to lie in pain listening to other women groaning and calling out in pain all down the corridor. I was very very scared! During the last few hours, after calling for a nurse for considerable time, she came bustling in and told me to 'shut up' and what did I expect when I was having a baby—of course I was in pain'. She then plonked the gas and air machine on my nose, told me the baby would not arrive for ages—and left me."

"Later in the night or early morning, another mother was admitted to the same ward and had her baby with just a screen between us. I was sweating with fear for my forthcoming labour, and it was probably far worse just to hear the sounds and not know what was happening. After this experience my own contractions stopped, probably due to fear."

"The first baby was born in hospital, the second at home. And the third will be at home. I found that in hospital they are more concerned with the second stage of labour than the first. The reasons may—in fact most probably are—due to shortage of staff, but to a woman giving birth to a baby—a first one in most cases—it is extremely terrifying to be left alone. I believe the staff in a maternity ward leave the women on their own for the simple reason that they do not know or understand how lonely they are. Shouldn't part of their instructions be the state of mind of a pregnant woman, as well as her body?"

"Why not make an appeal to women who have had at least three children, to volunteer to sit with mothers in labour wards of the busy maternity hospitals?"

"I had a midwife my age and two nurses present at my daughter's birth, and they were wonderful. We all worked as a team, and I can't speak too highly of them. My baby cried when her head popped out, and we all laughed, and suddenly the lump that I had in my tummy became a person. She was there and she was mine, and I was full of beans and wanted to rush around to all expectant mums to tell them not to fear, put themselves in the hands of their doctors and nurses, and enjoy the most wonderful experience of their lives."

"It is the adult approach that appealed to me personally. To be told encouragingly 'you are doing fine with your breathing, everything is coming along nicely' and 'now the second stage is starting, baby will soon be born'. You feel marvellous, as if you are part of the team, and they are rooting for you!"

"Looking back, it does seem to me the worst of childbirth is that the nurses and doctors tend to forget that you are the body through which life is coming into being, and that you want to be kept in the picture."

Some obstetricians and midwives still do not allow husbands to be with their wives during any stage of labour. Here are some more patients' views:

"Every woman realises that her husband is rather apprehensive the first time when he knows that his wife wants him with her, but it means secretly a lot to a woman that he did not choose to shirk what she could not shirk either."

"My husband said, a few hours after our son's birth—I cannot imagine life without him now; he seems to have belonged to us for ever, seeing him born made him belong to me, too, whereas, when you came home from the hospital with Sarah, she was a little stranger, and I found it hard to realise that I too had a place in her life."

"As for having one's husband at the birth, that's nonsense. Most men couldn't stand it, and that's a fact. My husband was visiting me when labour started, and I thought he would never go away and leave me to it. I can't be bothered with anyone during labour. In fact, I usually doze until it's time to start pushing."

If a husband wants to be with his wife in labour, I am certain that we have no right to deny him this experience. I actively encourage husbands to be present providing they know what to expect.

The following extracts describe the mothers' reactions after the baby has been delivered and in the puerperium:

"When at last I got to the ward, I thought I should see my baby, but they just said, 'he's all right, you'll see him in the morning'. Eventually one sympathetic staff nurse carried him round the ward and I saw him in her arms, but I still didn't have him to hold myself until the morning after he was born (he was born at two in the afternoon). All the ten days I was there, I only held him for a short while for feeding and when I eventually got home, it was some while before I felt he was really mine. My husband, too, had only seen him at a distance, he felt stranger than I did!"

"After each feed in hospital we were expected to express any milk remaining in the breasts, and woe betide us if, when the bowls were handed in, we had not contributed something. It was common practice for the midwife to take the mother's nipple between none too gentle fingers and to painfully extract such milk as remained in the breast. I don't condemn this practice, which seemed to help the breasts from becoming too heavy and painful, but I do object to the manner in which it was carried out. The hospital was modern, efficient, bright and cheerful, but we might indeed have been cattle—and rather tiresome cattle at that. I have no doubt that the nurses and midwives were overworked and the hospital understaffed—and perhaps in these conditions it is hard to be patient with mothers, who, after all, are not ill."

"The nurses should remember that although they are used to the sight of the human body, to many young women, childbirth is their first experience of hospital, and they are extremely shy of exposing themselves."

DISCUSSION

These extracts are only a small sample of the many views which were expressed in the different letters. Perhaps I have painted the picture in too harsh colours, but I feel that if we are really honest, we must admit that there are times when the atmosphere in our maternity units is not very pleasant. The recurrent theme of the letters is lack of rapport between the hospital staff and the patient, and we should do well to consider the reasons for this.

Why are some women left alone in labour and often shown very little kindness and sympathy? Why is there so little thought for the mother as an individual? How far is this situation the end-result of poor training and can it be prevented? Is this unsympathetic attitude a form of defence mechanism against the constant load of anxiety inevitable in every maternity unit? Is it also related to the fact that midwives have to work very hard for long periods under stress, and have to spend valuable time on domestic chores rather than on the actual care of the patients? Nurses in training always seem to be walking about and are seldom encouraged to sit down and talk to their patients. Does this also contribute to the later development of an inhuman attitude?

Why do some hospital doctors appear cold and distant? Are they overworked or badly trained? Do obstetricians in training have enough opportunity to learn much about normal labour and do they develop much insight into women as women? Has the physician-accoucheur been replaced by the surgeon-accoucheur with little interest in normal labour? Do our senses become dulled by constant observation of childbirth? Are some people's reactions to childbirth subconsciously different from what they appear to be on the surface? In fact, do some nurses and doctors find childbirth repugnant and not something rather wonderful? Do midwives who are spinsters past the menopause have to contend with specific emotional complications, which in part are exacerbated by their occupation?

How far are any of us fully aware of the impression we make upon the patient?

Major conflicts do often exist between midwives and doctors, midwives and midwives, and finally between trained midwives and pupils. It is useless for us to pretend any longer that these conflicts do not occur. Does the present training as laid down by the Central Midwives Board really encourage the idea that midwives should cooperate fully with doctors in the joint management of normal labour; or do the present regulations tend to encourage the midwife to think that she is entirely responsible for normal labour and need only call in medical aid (doctors) when things are going wrong? What other factors have resulted in doctors not being present during, or in control of normal labour?

Do the present training methods ensure that matrons, superintendent midwives, and sister-tutors have adequate knowledge of psychology and of the enormous influence that they may have for good or ill on young pupil midwives, who are often coping with emotional difficulties and complications of their own? In fact, should there be an " agonising re-appraisal " of all the present methods of training midwives and obstetricians?

Surely it is not necessary to know the answers to all these questions before we make some attempt to put our house in order. First, all hospital staff must appreciate that the mother-to-be is extremely vulnerable. She is at their mercy for good or for ill. Many of our present procedures, which involve dragooning and regimentation, must be revised. The training of nurses, medical students, and midwives must include a careful study of patient-staff relations and also exactly where these are likely to break down. The importance of *words* and their impact on the patient must be repeatedly emphasised—in particular the extraordinary value of kindness.

We must destroy the illusion that the patient is a human being apart, someone quite unlike ourselves. We must get rid of that awful method of dividing patients into " cooperative " or " uncooperative ", into " easy " or " difficult ". This classification is largely based on how much regimentation the patient will stand without complaining.

I have an enormous respect for the great work that midwives are doing, and the huge burden they are carrying, but I am conscious that there are a few midwives, just as there are doctors, who do let the side down badly. All midwives and doctors, particularly those in charge of labour wards, should have a proper insight into the emotional as well as the physical needs of their patients and staff. We must somehow ensure that no patient is ever at the mercy of a midwife's own frustrations and mixed-up emotions. No senior sister must be allowed to exert her authority by means of a reign of terror, to which even the consultant obstetrician himself sometimes submits.

We must replan our maternity units, so that every department reflects joy rather than sorrow, hope rather than gloom, life rather than death. Somehow we must contrive to reproduce in hospital the natural tranquillity that often develops quite spontaneously with home confinements. Architects must combine with us to experiment in new forms of design.

We must also resolve the conflicts which often exist between midwives and doctors. An obstetric unit must operate as a unit and not as a collection of jealous individuals. The division of obstetrics into " normal " and " abnormal " can only do harm, since obstetricians have come to concentrate their attention more and more on the abnormal. As a result so-called " normal " labour is taken for granted and is conducted on a rule-of-thumb conveyor-belt system. Obstetricians should take much more active interest in the direction and coordination of their units, for a maternity unit is a complex organisation, which calls for continuous leadership and example. Each unit must be encouraged to develop its own philosophy and sense of purpose. Obstetricians were not meant to be reluctant foremen of baby factories, but privileged guardians of the next generation.

If we can use pregnancy as a time of preparation, not only for labour but for all that family life means, and if we can make childbirth a more positive experience, then I think the social repercussions will be remarkable. The next century will undoubtedly see a great advance in our understanding of all the complex factors that influence and govern human relationships. The health, happiness, and possibly even the survival of our children will depend on the success of our studies in this field. Midwives and obstetricians have an especial responsibility, for they are there at the beginning, and probably it is the manner of the beginning that matters most of all.

The Widdicombe File

LX.—ON AUTHORSHIP

DEAR GEORGE,

I said I'd tell you how to get a paper printed, and do it I shall. There are two approaches and I'll give you the most dangerous first: "27-Oxyhydro-10 Propolapine and its Linkage with an Aliphatic Chain in the Gunner-Bungstadt-Freundloichter Syndrome". You'd think you would be safe with that (this is for the glossy magazines, by the way, the ones which come flat); but somewhere there will be an expert on 27-0-10-P and he'll want to know how you got the aliphatic linkage when he always uses a hydroxyl grouping. It's no use returning his letters with "gone away" or "do not wish to join": when he tracks you to St. E's you'll have to lock yourself in the lavatory. So we'd better get back into the "popular price" class, as the motorcar people say.

What about "Steady Increase in the Number of Two-Headed Men seen at an Outpatient Clinic in the South London Area"? You'll have the field pretty well to yourself, and other two-headed doctors (I mean one-headed doctors of two-headed people) will be cheerful extroverts. Subsequent correspondence with them will be chatty and gossipy. You'll have fun with the record companies who'll want you to form close-harmony groups (four for the price of two).

You rather like this one? All right. Your facts and figures are marshalled (including those who didn't come back but should have) and you are now ready to communicate with an anxiously awaiting world.

The original title is a bit long. What about "Increase in the Number of Two-Headed Men in the South London Area"? This is nicer but it might not be quite true. Perhaps the population is steady and more are coming to the clinic. What about "Two-Headed Men"? The papers would call this a banner line, and it has the impact (slightly subdued) of "Blonde Slugs Cop With Bottle" which I saw in New York before the war.

Now comes the framework of the paper. If you don't rough it out beforehand you may get the results mixed with the method, and other combinations which will give the thing a "jumpy" feel.

Next the introduction—the "why" of the paper. "My wife won't let me watch Wagon Train and Gun Law on the telly; so I am writing this paper on two-headed men so that she will see my suffering and relent." This, of course, might be quite honest and will get you the manuscript by return, a gold medal from the editor with his sincere admiration for the truth, and a visit from a psychiatric aftercare worker. So you can cut out the family life bit. Normally the introduction leads from the title into the body of the paper. I notice that occasionally a piece of the discussion strays into it and sometimes the two are combined. I suppose this is permissible if it more fully describes what the paper is about, but I prefer to bare my soul at the outset and let them have the facts and figures early on.

The next phase is material and methods. If you intend to write a series of papers these will have to be described in detail in the opening number and you can refer back in subsequent productions. Whether you include them or not in your final copy, subheadings are essential in your earlier runs. It will let you visualise the paper throughout. Clinical Material describes what you are working with:

"The patients formed a group seen at a special outpatient department serving a general population of 100,000 in the South London area."

What you did with them will come next, under Clinical Methods:

"The patients were interviewed by the almoner at first attendance and an individual punch card was made out on which were recorded weekly, weights, blood-counts, and gastric acidity findings."

Now comes Laboratory Methods:

"A sample of bile was obtained from each patient by duodenal intubation when first seen and weekly thereafter for three months. These were stored in the cold cabinet of a domestic refrigerator until the completion of the investigation when they were tested by the method of Jekyll and Hyde (1950)."

I now use Clinical and Laboratory Methods as one subheading, and include in it material and clinical and laboratory methods. It saves space and it seems to read quite clearly.

And now comes the meat of the paper—what you found. This should be subtitled Clinical Findings, or Results if you prefer. Graphs should only be used if they assist clarity and you should be able to save space in the description. But a clear table of results makes the paper easy to read and is handy for reference. The same holds good for laboratory findings, which usually tabulate well.

Now for the Discussion. You can let yourself go a bit here as you have been somewhat Spartan (as you should) in your material, methods, and findings. Discuss the background to your paper more fully, and bring in similarity or otherwise to previous investigations with the references. Having done so, lead on to what you think has been suggested or proved from your paper, and there you are. This last bit is sometimes subtitled Conclusions; but I think the reader will draw his own conclusions and you should always underestimate the importance of your findings rather than otherwise.

The Summary, which comes next, is a bare-bones recapitulation of the facts and findings. Nothing new must be added. Acknowledgments now follow, and there can be very few papers which are the sole unaided work of one man. A word of thanks to those who helped is not out of place.

References come last, and use as few as possible. If you are writing a thesis or a book, then of course you will try to include everything which has a bearing on your investigation.

Well, George, these are the "Easy steps to authorship" and they would apply equally to a short paper or a book. I find it useful to have the references before me at all times, and I got our carpenter to put a large notice-board in the office on which I pin abstracts of relevant papers. It saves shuffling through a file each time you want something.

Now let's get right back to the beginning and commence the actual writing. There is a tendency which we all share when writing for publication to be somewhat pompous and prosy: "We have been reluctantly forced to the conclusion after careful and prolonged deliberation that"—which only means "We think" or "It seems". Semantics is the science of the meaning of words, and the reader should know what you are saying at first pass.

So keep your writing simple. The sentences should be fairly short and should follow each other smoothly. Remember you are not reporting a prize-fight:

"Have seen 80 cases G.B.F. syndrome . . . given one half 27-0-10-P, the other half chalk . . . half with 27 &c O.K., other half gone . . . useless writing . . . am changing name and leaving country."

As regards punctuation don't bother about it too much. Get the periods in as you write and you can deal with the commas later.

Some people still write in longhand, but for many years I have typed the papers from the first copy; otherwise I have no idea what it will look like in print. If you are writing with a pen, feed it to your secretary as you finish each page. You will get the feel of it earlier and it will save space on your desk.

Let's suppose you have finished the first copy and you are wondering whether to burn it or plug grimly on. What about your figures; don't you think a statistical analysis would be a good thing? This is where you meet statisticians for the first time, and there's quite a technique for this. At first contact you will be asked if you use the χ^2 technique, and you will answer simply (and truthfully) "I dunno, I never was any good at sums". You will then find them very pleasant, and as a rule they won't knock the figures about much. Their advice is helpful in the preparation and presentation of tables.

That's another hurdle behind you. Still want to go on? I know you hate the sight of the thing by now. Already you are on conversational terms with trees, birds, and telegraph poles: in public transport your lips move soundlessly and you don't seem to have much recollection of how you get home at nights. But there is one other thing I must mention and that is tense. When your nerves have calmed a bit go through the paper and see you are not switching from past to present: perhaps better still, get someone else to do it to whom the paper is new. On the whole it's better to keep everything in the past tense.

Now the paper is finished and this is the next essential move. Put it in a drawer and forget about it for a month or two. All papers improve with ripening, and this is the time for you to get out and about, meet people, ignore the birds. Some time when you have recovered, get the paper out and go through it with a black wax pencil. Don't be frightened, it will have to be retyped about ten times anyway. Cut, cut, and cut each time. You say there will be nothing left; but a small diamond is better than a ton of household coke, so get in there and slash.

Dawn follows the night and you are now coming up for the final retype. By this time your secretary will have resigned three times and no-one has smiled for weeks, but this is the copy which must be perfect. Feed it to her a sheet at a time and go through it with a comb for spelling and punctuation. Keep two copies yourself. Sometimes you can erase a spelling error without altering the appearance of the sheet, but if it looks messy have it retyped. Remember, at every retyping there's a chance of a spelling error creeping in. Double spacing, by the way, with a good margin. At this stage I detach a copy of the references and get our librarian to check them. He also abbreviates the titles of the journals for me.

And now here it is at last. A slim edition of its former self (and much better too). Keep it in an envelope; it looks better without dog ears and teacup stains. I post my MS flat in a foolscap envelope and clip a short letter to the editor on the front.

Suppose all has gone well: your article is accepted; and the great day comes. Let's follow *The Locust* into a typical medical household. It's father's day for the atomic space gun, and from behind his coffee he's having a surreptitious shot at the fireplace to see if it really disintegrates; mother is looking wistfully at the incredible figures in *Vogue*; and young Alfie is taking swipes at his brother with *The Locust* until told to "put it with your father's other medical magazines" (in the toolshed), and there it stays until the next Comanche raid by the redskins across the road. It's a very handy size for frontier warfare. In the seats of learning a few may tick it for future reading and fewer still may actually read it after a glance at the summary. A very (very) few may be interested and may actually ask you for a reprint. Now I am firmly of the opinion after careful and prolonged (Good God, I'm doing it too)—well I think that all these letters and cards should be answered personally. I feel that this is common politeness. After all, the mere fact that they have written to you is a compliment, and a cold-blooded reprint without a personal note is somewhat inhuman. Although of a retiring and introverted nature, on this point I am willing to take on all comers. In this troubled age a return to the courtesy of more leisured times is all the more essential.

Still want me to look at your paper?

UNCLE M—.

Medicine and the Law

Effects of a Plastic Operation

ON Dec. 10, 1952, a plastic surgeon performed an operation to remove excess fat from beneath both eyelids of a 29-year-old woman outpatient. Before she returned home the patient received certain directions from the surgeon, who also told her the telephone number of his consulting-rooms and arranged to remove the stitches on the sixth day. The patient subsequently developed lumps below both eyes. She sued the surgeon alleging, inter alia, negligence in the postoperative treatment. The allegations were denied.

Mr. Justice MCNAIR, awarding the patient £1408 damages, said that the defendant was a well-qualified plastic surgeon; he shared with another surgeon consulting-rooms and the use of a secretary, and at this address there was a resident janitor and his wife. His Lordship accepted that the surgeon, on being told that the patient could not afford his usual fee and additional nursing-home charges, had reduced the fee to 10 guineas inclusive on the basis that the operation would be done under a local anæsthetic and that she would be an outpatient. No charge of professional negligence could be made against the surgeon solely on the ground that he had not insisted on retaining the patient in a nursing-home after the operation, although it was clear that this course involved some increased risk. No criticism was directed to his technique for this operation. It was clear that the first 48 hours were of crucial importance as bleeding might occur and, if not attended to properly, irreversible damage might result. It was on the failure to carry out sufficient aftercare that the patient's case rested.

If a patient was operated on and then allowed to go home, proper directions should be given by the surgeon

to the patient (as had been done in this case) and the surgeon himself, or a properly qualified substitute, should be available and accessible to deal with any untoward development until the patient's next appointment. If the surgeon was relying on a telephone message from the patient to deal with an unexpected emergency it was essential that the telephone should be adequately covered in the sense that messages would be received and transmitted to the surgeon. That had not been done in this case. On the first day after the operation there was substantial bleeding from the stitches, which continued intermittently for a day or so. Proper notification of the bleeding was communicated by telephone to the number which had been given, but such notification was not received by the surgeon. His lordship held that this was due to the surgeon's failure to keep his telephone adequately covered, or the failure of those for whom he was responsible to inform him of the message. That failure amounted to professional negligence.

His Lordship had reached the conclusion that the condition from which the patient now suffered was directly caused by the failure to deal with the initial bleeding within the first 48 hours, and accordingly the defendant was liable.

Corder *v.* Banks.—*Queen's Bench Division* (McNair, *J.*) April 8, 1960. Counsel and solicitors: F. W. Beney, Q.C., and Arthur Mildon (Kenneth Brown Baker, Baker); Martin Jukes, Q.C., and Peter Webster (Hempsons).

EIRA CARYL-THOMAS
Barrister-at-Law.

Interruption of Continuous Care and Treatment

A husband petitioned for divorce on the ground of his wife's incurable insanity. The answer put forward was that the requirement that the wife must have been continuously under care and treatment for at least 5 years immediately preceding the presentation of the petition was not fulfilled.

The marriage took place in 1948. In November, 1952, the wife was admitted to St. Ebba's Hospital, Epsom, as a voluntary patient, with schizophrenia. She remained there until May, 1955, when she was taken to Cheam Sanatorium for treatment for tuberculosis. She remained in Cheam Sanatorium for 11 weeks, and then, owing to a deterioration in her mental condition, was readmitted to St. Ebba's as a voluntary patient and had remained there ever since.

Mr. Justice LLOYD-JONES said that to succeed, the husband must prove (i) that at the date of his petition the wife was incurably of unsound mind, and (ii) that at that date she had been continuously under care and treatment for at least the immediately preceding 5 years. The first of those requirements had been proved, but a difficulty arose on the second.

Under section 1 of the Matrimonial Causes Act 1950, a person of unsound mind was deemed to be under care and treatment while being treated as a voluntary patient, provided such treatment followed without any interval a period during which the patient was detained as a certified patient. As the wife in this case remained throughout a voluntary patient, that requirement was clearly not fulfilled. That Act, however, had been amended by the Divorce (Insanity and Desertion) Act 1958, so as to extend its operation in several important respects. Thus, as a result of the 1958 Act, a person was to be deemed to be under care and treatment at any time when he was receiving treatment for mental illness " as a resident in a hospital or other institution provided, approved, licensed, registered or exempted from registration by any Minister or other authority in the United Kingdom, the Isle of Man or the Channel Islands ". Again, treatment as a voluntary patient now sufficed, without the necessity of a preceding period of detention under certification.

Although, therefore, the husband was not confronted with any difficulty arising from the fact that the wife was throughout the material period a voluntary patient only, in his Lordship's view, the phrase in the 1958 Act " resident in a hospital . . . provided . . . by any Minister " must be construed to mean a hospital provided for the purpose of giving mental treatment. The evidence had established that while St. Ebba's was a mental hospital, Cheam Sanatorium was used solely for the reception and treatment of tuberculous patients. Moreover, in connection with the wife's stay at Cheam Sanatorium, she had been required to discharge herself as a voluntary patient from St. Ebba's in May, 1955. As a result, she ceased, for the 11 weeks during which she was at Cheam, to be on the books of St. Ebba's. This distinguished the case from that of Swymer *v.* Swymer, decided in 1955, in which a husband who was a voluntary patient in a mental hospital was sent for 4 months to another hospital for treatment for a fractured leg, but his name remained on the books of the mental hospital during his absence, and it was held that that fact prevented the 5-year period from being broken. His Lordship therefore held that the 5-year period in the present case had been broken for 11 weeks. Although the 1958 Act provided that in determining whether any period of care and treatment had been continuous, any interruption of such period for 28 days or less should be disregarded, the 11 weeks' interruption was fatal. The petition was therefore dismissed.

Mesure *v.* Mesure—*Probate, Divorce & Admiralty Division:* Lloyd-Jones, *J.* April 1, 1960. Counsel and solicitors: G. H. Crispin and H. B. Figg (Culross & Co.); R. B. Holroyd Pearce and N. A. Medawar (Official Solicitor as guardian *ad litem* for the wife).

D. R. ELLISON
Barrister-at-Law.

Abnormal and/or Depraved?

Patrick Joseph Byrne, a 29-year-old labourer, entered a women's hostel, strangled a young woman, and decapitated the body. The victim was apparently a stranger to him.

At his trial on a charge of murder, the defence asked the jury for a verdict of manslaughter under the Homicide Act, 1957, on the ground of diminished responsibility.[1] The defence called a psychiatrist, who said that Byrne was abnormal rather than depraved.

Commenting on the medical evidence, Mr. Justice Stable said he could not see why a man could not be abnormal and depraved. " There is a distinction between the two words, but does the one necessarily exclude the other ? " His Lordship went on to say that he would give the jury a direction on law which, if it was wrong, would be corrected by the Court of Criminal Appeal. The relevant section of the Homicide Act was, he said, new in English law. " It is a mercy section intended for the protection, for the alleviation, of a man who has done a criminal act whose condition does not bring him within the McNaughten rules, but who mentally is not quite as other men are ".

The jury would consider whether the object of the section was to provide some additional protection to the utterly vicious or whether the object was to provide some protection for the mentally afflicted. " If the legislature had intended that a man who strangles a woman under the influence of overwhelming violent and perverted lust should be immune from the ordinary consequences of his act it would be so simple to pass an Act of Parliament in those terms. They have not done so. If there is evidence which leads you to say this man is not responsible, as other men are, for the full consequences of what he did—if there is nothing else then I say the vicious, depraved tendencies, thoughts, desires, lusts and conduct do not bring the accused within the section and that does not constitute

1. *Times*, March 25, 1960.

such abnormality of mind as substantially to impair his mental responsibility for his acts ".

The jury returned a verdict of guilty of murder, and—since the offence did not constitute capital murder—Byrne was sentenced to life imprisonment.

It is understood that Byrne has appealed to the Court of Criminal Appeal, and comment on Mr. Justice Stable's summing up must await the outcome of that appeal.

Symposium

FORMATION AND BREAKDOWN OF HÆMOGLOBIN

A SYMPOSIUM on this subject was held at the meeting of the Association of Clinical Biochemists, in conjunction with the Biochemical Society, at Leeds on March 26. Dr. C. P. STEWART and Prof. G. H. LATHE presided.

Iron Incorporation in Hæm Biosynthesis

A. GOLDBERG (Glasgow) said that an in-vitro method had been established by means of radioiron (^{59}Fe) whereby the enzymic incorporation of iron into protoporphyrim, an intermediate in hæm biosynthesis, could be accurately measured. An aqueous " particle-free " extract of chicken erythrocytes contained an iron-incorporating enzyme (I.I.E.). This extract could be separated by ultrainfiltration into two fractions, a residue which contained the enzyme and an ultrafiltrate which markedly potentiated the action of the enzyme. The ultrafiltrate contained dehydroascorbic acid, glutathione, and ergothioneine in concentrations of the same order as were found in human erythrocytes and in these concentrations each of them potentiated the effect of the enzyme. Homogenates of human and rat liver, kidney, and spleen, and of human bone-marrow and reticulocytes were also sources of I.I.E. A spleen which showed histological evidence of extramedullary erythropoiesis had an enzymic activity nearly four times greater than that of one without. Dialysis of these tissue homogenates against water led to a marked loss of activity as well as a considerable reduction in their contents of ascorbic acid and glutathione (G.S.H.). Enzyme activity was restored on addition of ascorbic acid or G.S.H. to the dialysed extract. Of the intracellular components of human and rat liver the mitochondria were the richest sources of I.I.E.—a link with the finding of Bessis and Breton-Gorius that ferritrin iron is mainly concentrated in the mitochondria of the hæmoglobin-forming erythroblast. The enzymic activity of the mitochondria was also potentiated by the addition of ascorbic acid and G.S.H. Further studies had shown that these physiological reducing substances rendered protein-bound iron available for hæm biosynthesis. Radioiron was incorporated into rat plasma and liver and human serum. The radioactivity was shown to reside in the β-globulin suggesting the radioiron was attached to siderophilin. Ascorbic acid and G.S.H. facilitated the transfer of radioiron from human or rat siderophilin and also from rat-liver homogenate for its enzymic incorporation into protoporphyrin, the concentrations which did so being within the ranges of those which occur in human as well as rat liver. Thus these substances played a part in the transfer as well as the utilisation of iron.

Role of Conjugation in the Excretion of Bilirubin

BARBARA H. BILLING (London) said that excretion of bilirubin in the bile or urine was only possible if it was first converted to a water-soluble derivative. In mammals the most important conjugates seemed to be the ester glucuronides; sulphate was also formed and there was evidence for small quantities of other unidentified conjugates. Conjugation took place in the liver microsomes as the result of the enzymatic action of a glucuronyl transferase with uridine diphosphate glucuronic acid (U.D.P.G.A.) acting as the glucuronyl donor. Extrahepatic conjugation had been demonstrated in vitro and in hepatectomised animals but it was not known if this was important in normal subjects. The capacity of the liver for conjugating bilirubin in adults was considerably greater than that normally required for the excretion of the breakdown products of hæmoglobin. In hæmolytic disease, however, this may be exceeded so that mild jaundice occurred. Impairment in the conjugation of bilirubin resulted in its accumulation in the body so that both tissues and plasma became icteric. This may be due to a deficiency of glucuronyl transferase such as was found in the newborn and was responsible for the development of " physiological jaundice ". This enzymic defect was also found in patients with the severe type of hyperbilirubinæmia first described by Criggler and Najjer and in Gunn rats. In mild forms of congenital hyperbilirubinæmia (Gilbert's disease) the raised serum-bilirubin levels could not be explained by an enzyme deficiency and a more likely explanation was a reduced hepatic uptake of bilirubin from the plasma. Although conjugation was essential for the secretion of bilirubin by the hepatic cell, it was not necessarily the limiting factor. In the Dubin and Johnson, and Rotor types of familial hyperbilirubinæmia, in which there was no evidence of intrahepatic or extrahepatic obstruction, both conjugated and unconjugated bilirubin accumulated in the plasma. There therefore appeared to be a specific defect in the secretion of conjugated bilirubin the mechanism of which was not known. In the newborn this mechanism may be slow to develop since in a few families, who had received exchange transfusions as treatment for erythroblastosis, it had been observed that, during the recovery period, conjugated hyperbilirubinæmia developed. At present little was known of the mechanism of excretion of conjugated bilirubin by the kidney. Tubular secretion had been demonstrated, extremely low clearance figures were obtained in hepatitis and obstructive jaundice and these varied considerably during the course of the disease.

Effect of Icterogenin on Biliary Secretion

C. RIMINGTON, T. HEIKEL, B. C. KNIGHT, E. J. WILLIAMS, and H. D. RITCHIE recalled that in 1937 Rimington and his coworkers studied a disease in South African sheep which was characterised by icterus and photosensitisation phenomena. They showed the disease could be reproduced by the administration of extracts from the plant *Lippia rehmanni*. The active agent was isolated and found to be a triterpene acid, which they called icterogenin. This inhibited bilirubin excretion in some animals, without concomitant evidence of toxic liver damage. It was thought a closer understanding of the mechanism whereby icterogenin produced this effect might help to illuminate some cases of human jaundice. The rabbit was found to be the only suitable experimental animal. Biliary fistulæ were created by cannulating the common bileduct and ligating the cystic duct, and the toxic agent was introduced into the peritoneal cavity. The technique used produced regularly a colourless bile within 8–24 hours, usually followed by recovery over the next 2–3 days. In a rabbit dosed with icterogenin, bile volume was much diminished; bilirubin, bromsulphalein, coproporphyrin, and phylloerythrin excretion were suppressed during the stage of action of the drug, excretion of them then slowly returning. Alkaline-phosphatase excretion was affected to a much smaller extent, if at all, and bile salts were present in significant amount. Histological examination revealed no distinct abnormality. Reverse-phase chromatography of the pigments in the serum of the dosed rabbits showed an accumulation of pigment I. The possibility that icterogenin suppressed bilirubin and bromsulphalein excretion merely by interfering with conjugation may be rejected, firstly, since different conjugates were involved, bilirubin with glucuronic acid and bromsulphalein with aminoacids, and secondly, since rabbit bile, rich in bilirubin diglucuronide, when injected intravenously, was not excreted by the icterogenin-poisoned animal. Reviewing all the experimental findings, a possible hypothesis might be that mild intoxication with icterogenin caused a slowing of the passage

of the test substance through the liver cell. Higher doses may temporarily inhibit biliary excretion, probably owing to altered permeability of the cell membrane facing the bile canaliculus. Bile accumulated in the liver cell and may be segregated in vacuoles or it may ultimately flood the cell and pass through the cell membrane into the sinusoids. These changes do not produce histological findings visible by conventional techniques.

The Urobilins

D. NICHOLSON (London) said that the urobilins and their colourless dihydro derivatives are the ultimate products of biological reduction of bilirubin glucuronide. Only *i*-urobilin has a structure fully established by degradation and synthesis; it is usually formulated as *bis*-hydroxypyrrole. Until 1958 only two other members of this class of pigment were known—stercobilin and *d*-urobilin, shown to be tetrahydro and dihydro derivatives respectively of *i*-urobilin. So-called "hydroxypyrroles" have been shown to exist in a pyrrolenone form and bile pigments in general may be assumed to have *bis*-pyrrolenone structures. A *bis*-pyrrolidone structure for stercobilin has been established. Some progress towards elucidation of the structure of *d*-urobilin has been made, and these studies suggest that the pigment differs from *i*-urobilin by containing a centre of unsaturation attached to, or in, one ring. From tetrahydro-*d*-urobilin a new *d*-rotatory isomer of *i*-urobilin (*d*-urobilin-IX α) has been obtained. On classical views, tetrapyrrolic *bis*-hydroxypyrrole compounds would not be expected to show optical activity; the existence of *d*-urobilin-IX α was therefore considered additional evidence for a *bis*-pyrrolenone structure for *i*-urobilin. Optical rotatory dispersion studies suggested, however, that asymmetric carbon atoms were not the sole source of optical activity in these pigments. Comparison of oxidation products of *i*-urobilin with those of *d*-urobilin and its derivatives indicated the possible existence of geometrical isomerism in these compounds. Recent theoretical studies revealed a higher electron density at the α-methene group of protoporphyrin IX than at the other three methene groups. Protoporphyrin may therefore be expected to undergo fission preferentially at the α position and all natural bile pigments should have the "IX α" order of β side chains exclusively; this had been confirmed by degradation of the pigments to pyrrolic acids.

Public Health

Statistics for 1959

England and Wales

Provisional figures issued by the Registrar General [1] show that last year the death-rate from all forms of tuberculosis was 85 (respiratory 77) per 1,000,000 population. The death-rate from cancer of the lung and bronchus in men was 831 per 1,000,000 population (784 in 1958) and in women 123 (119 in 1958). In males deaths from this cause accounted for over 35% of all deaths from cancer; in women this proportion was just over 6%. The provisional maternal mortality-rate was 0·38 per 1000 live and still births (0·43 in 1958) and the neonatal mortality-rate was 15·8 per 1000 live births (16·2 in 1958).

Eire

In Eire last year the death-rate was 12·0 per 1000 population, which was the same in 1958.[2] The death-rate from all forms of tuberculosis was 0·18 per 1000 population. The maternal mortality-rate was 0·66 per 1000 births registered, compared with 1·03 in 1958; the infant-mortality rate was 32 per 1000 births registered (35 in 1958) and the neonatal death-rate was 21 (23 in 1958).

Census of Population

The date of the next Census in Great Britain is Sunday, April 23, 1961.

1. Registrar General's weekly return for England and Wales: week ended April 2, 1960. H.M. Stationery Office. Pp. 20. 1*s*. 6*d*.
2. Quarterly report on births, deaths, and marriages, December quarter, 1959, and yearly summary, 1959. Dublin: Government Publications Sale Office. Pp. 78. 6*d*.

In England Now

A Running Commentary by Peripatetic Correspondents

"WHEN I borrow money from you," said Ananias plaintively, "you might at least provide new banknotes. This one resembles in all but value a dilapidated Dead Sea scroll. I ask you to believe that my interest in 'crinkle' is purely æsthetic, like that of my cousin Fred who for several months provided a valuable public service as a peripatetic bureau-de-change outside Victoria station.

"In exchange for their native currency, unwary travellers received neatly wrapped bundles of used London Passenger Transport tickets, under the impression that they were a new issue of English banknotes. Fred put it very beautifully when he said that the rapacity with which some people plunged into such black-market currency dealings filled him with a sadness that resembled sorrow as the mist resembles the rain. It was probably because of the mist that he failed to see a policeman coming and felt in consequence compelled to change his business address for one in a less damp climate.

"Unluckily his collection of tickets did not include one for the boat, which he was persuaded to leave in Barcelona; or for the bull-fight which he was compelled to leave in Madrid. Furthermore, the manager, who must have kept a diary, remembered being a customer of Fred's at Victoria, and was so uncharitable in his attitude to Fred's story about searching all over Spain to give him his money back that Fred climbed over the wrong wall and found himself in the bull-ring. His appearance caused some confusion, during which two bulls got loose at once and charged him from the N.E. and S.W. simultaneously. Fred achieved a last-minute vertical take-off that would have gladdened all hearts at Cape Canaveral, and the two animals collided and knocked each other unconscious.

"The novelty of this spectacle appealed to the audience as much as its economy appealed to the manager, who realised that the bulls—and if he was nippy enough, Fred—could be used next time, and sooner than disappoint his (the manager's) public, decided that Fred would perform every evening at seven, matinees Tuesdays and Saturdays.

"After a time, however, the bulls must have started comparing notes, and although they never understood the situation, they decided that if a matador was so unsporting as to fill his hip-pocket with flat-irons, they wanted nothing further to do with him, and Fred received notice in lieu of a week's salary. He had the best of the bargain as he wasn't being paid anyway, but what with keeping his eye on the bull—or rather on two bulls—he developed bull-fighter's nystagmus and was run out of town by indignant Spaniards who thought he was ogling their women-folk.

"A firm of travel-agents called INTERPOL arranged his passage home and a period of two years' convalescence. Unhappily it was of no use, because soon after he came out Fred died of overwork. He had been in partnership with a man who made model ships in bottles, and it was Fred's job to empty the bottles."

* * *

It is impossible to foresee what the world will be like in the year 9000, but harmless to speculate. Despite the 350 world wars which are statistically predictable and which will have helped to reduce world population by that time, the population of Australia alone will then stand at about 400 million people. Let us suppose that in the third millennium an error in the calculation of the trajectory of an atomic missile, caused by metal fatigue of an electronic brain, exposed the whole eastern seaboard of Australia to sublethal irradiation. As so often in the course of history, this seeming catastrophe proved to be a blessing in a country whose chief source of food had now become the sea.

This unplanned irradiation produced a number of favourable as well as unfavourable mutations. One of the more favourable was that in a certain number of people the proerythroblasts lost their ability to distinguish between the metals, iron and magnesium, which ability had hitherto been essential to the

synthesis of hæmogloblin. Nevertheless, the fortunate possessors of these unique proerythroblasts developed a bone-marrow which produced not only white cells and red cells but also green cells. The chlorocytes, when activated by the sun's rays, were capable of synthesising carbohydrate. Thus the simple expedient of exposing the body to the sun's rays on Bondi Beach became a method of sustaining life, and one to which the Australian population was peculiarly adapted.

Undesirable animal mutants occurred, such as meat-eating cattle; but some sheep and cattle were bred which had also a quota of chlorocytes in their bloodstreams. These animals no longer required grass, but, with a plentiful supply of sunshine and water, were able to manufacture their own foodstuffs. The cattle and sheep were kept in paddocks paved with green concrete, since sentiment is a powerful emotion. When left alone, the cattle grew and fattened without any great attention except for an occasional spraying in order to keep off the green aphids.

The world became an easier place to live in, except for one small thing. Many people and animals developed psycho-neuroses, since they were deprived of the one function in which they had most delighted to indulge—eating.

* * *

I was very pleased to get an office at all when I moved into the new unit, but I did not expect to have to share it with a ghost. For the first few days I did not realise that it was haunted, but when I decided to make some improvements the trouble started. I began by negotiating with the secretary for a clean piece of blotting-paper. It shone splendidly on my desk for a day; but when I came in next morning the blotting-paper was decorated with a lively drawing of the head of a devil, boldly executed in my black ink. I turned the paper over, since hospital policy does not allow me a clean piece of blotting-paper more than once a week.

My next attempt to improve the amenities was to ask Sister for a second armchair. The one already present was on the patient's side of my desk, and I saw no reason why I too should not relax during interviews. My ghost thought otherwise. Next day the chair had vanished. I reclaimed it from the lounge and pinned a notice to it: "Please do not remove this chair." The chair has remained, so I assume that my ghost is literate. It seems indeed to be not only literate but educated, since in my desk drawer yesterday I found a copy of Plutarch's *Essays*. This would not have been my first choice for passing the time, as I prefer Marcus Aurelius, but it shows a commendable breadth of interest. Today I intend to leave out a note with "1. P-K4" on it, to see what happens.

* * *

I know that psychiatry is not yet altogether respectable and in some minds is still associated with legerdemain or astrology, but I was a little hurt at a party the other evening. Drinks were liberal and my hostess became confidential. "Psychoanalyse me," she said: "I'm Pisces."

* * *

SALT RETENTION

Dear, do not weep—
Since recent years
It is more wise to keep
A watch on tears:

Some seek to analyse
With callow art
An easy pathway from your eyes
Into your heart

While others feel
That tears are nothing fine
And have no power to heal
More strong than lysozyme.

Besides, you should not grieve
But keep your sorrows pent—
There's not a man can quite forgive
Embarrassment.

Letters to the Editor

PLACENTA PRÆVIA

SIR,—Since 1947 not more than 30 and not less than 20 cases of placenta prævia have occurred in any one year in Bradford, so that the fœtal wastage from this condition is negligible compared with that from antepartum hæmorrhage sine P.P. I am, therefore, in complete agreement with Professor Macafee's views and share his high esteem for Dr. Blair Hartley's outstanding contribution to obstetric radiology.

I have ventured to enter this almost private controversy because it seemed to me that Dr. Blair Hartley, in his letter of April 9, inferred that maternal lives might have been lost because either the patients themselves or their doctors were afraid to avail themselves of radiological investigations.

We used to do X-ray pelvimetry on over 300 patients each year, together with a goodly number of placentograms. Some three years ago my colleagues, Mr. G. A. Craig and Mr. A. C. Muir, and I decided (*a*) to stop mass radiography of the chest in antenatal patients and to substitute careful filming (and to stop even this procedure if the results failed to warrant it); (*b*) to stop X-ray pelvimetry and placentography; and (*c*) to limit the use of X-rays to confirming (or not) the diagnosis of fœtal abnormality, and of multiple pregnancy, and to determining the fœtal presentation in doubtful cases.

During the past nineteen months there have been over 8500 deliveries in the city of Bradford without a single maternal death, and it cannot, therefore, be argued that the abandoning of X-ray pelvimetry and of placentography has caused maternal loss of life. Neither do we think that any infant has been lost because of the above decision.

Dr. Blair Hartley admits that X-ray investigations may involve a slight risk to the fœtus; everybody is agreed that ionising radiations should be limited to the absolutely necessary level; and, it is suggested, the Bradford limitation on the clinical reasons for inviting examination by the X-ray method has not resulted in either maternal or fœtal loss of life, or an increase in the cæsarean-section rate.

Bradford. G. W. THEOBALD.

FLUORIDATION

SIR,—Dr. Dobbs (April 2) makes some statements which call for challenge. One is that there can be no direct evidence on the toxic effects of pollution unless experimentation is carried out on an impossibly massive scale. The context of the discussion is water, and solely for the purpose of the argument the view that fluoride is a pollution will not be here contested; it is pertinent, then, to point out that Nature has herself carried out the experiment which Dr. Dobbs considers impossible and that a mass of studies attest to the fact that use has been made of this. Again, Dr. Dobbs holds it as "mere speculation" that there is a critical level below which the fluoride ion loses its toxic character and becomes physiologically beneficial. Several other elements have a beneficial effect at low level and a toxic effect at high level—e.g., iron.

Does Dr. Dobbs propose that every drinking-water in the country should have its fluoride content removed, and if not, why not? Also, in his keenness to avoid an intake of this toxic substance does he avoid eating chicken at 1·4 p.p.m., liver at 1·5 p.p.m., lamb at 1·2, canned fish at approximately 4 or more, and honey at 1·0 part per million? Presumably he also avoids

drinking tea, which is quite a good source of fluoride too. Deprived of drinking tea he cannot turn to beer with confidence as this may contain approximately 1 p.p.m. of fluoride!

Discussions of fluoridation do not always centre on the dental aspects to the exclusion of a potential health hazard. At the Royal Society of Health Congress in May, 1957, there was a symposium on fluoridation and papers by Dr. W. Alcock and Dr. W. T. C. Berry which discussed public-health and toxicological aspects. Few if any papers on this subject by proponents fail to discuss the safety aspects.

When we learn from such a high authority as Prof. Hugo Theorell that "fluoride ion can inhibit lipase at 1 part in five million" we wonder why it is that the inhabitants of West Mersea, for example, where the water contains many times this concentration (5·8 p.p.m., compared with the more common 0·2 p.p.m.) are not all in hospital with steatorrhœa. Could it be merely that Professor Theorell's observation relates to in-vitro study, and that the in-vivo picture is quite different?

Public Health Department,
Bradford. C. L. SHARP.

SIR,—Dr. Dobbs is surely not on very firm ground in questioning the possibility of fluoride, though toxic in larger doses, being beneficial at lower levels of intake. Nor is he any more justified in claiming dental fluorosis, perhaps an unfortunate description, as necessarily a toxic manifestation.

Fluorine is invariably present to some extent in human enamel and in that context all human enamel can quite fairly be described as fluorosed. Where the drinking-water contains 1 p.p.m. F, the fluoride content of the enamel is higher, the enamel is better in quality and, in addition to being more resistant to decay, contains fewer developmental defects.[1,2] This can be seen in the Slough, Bucks, natural-fluoride area (0·9 p.p.m.) where no-one who has had the privilege of examining the children's teeth could fail to be impressed by the splendid quality of the dental enamel and in particular that of the incisors. Their beautiful colour and obvious high resistance to decay was to me little short of amazing. Clinical judgment, quite apart from any statistical evaluation, was sufficient to carry complete conviction.

Whether fluorine is in fact an essential trace element may be open to question, but Roholm [3] did call attention to evidence that fluorine was necessary for the maturation of rye, and other experiments have claimed to show reduced fertility in rats fed on a fluoride-free diet. Dr. W. T. C. Berry,[4] writing of the improved quality of dental enamel conferred by moderate amounts of fluoride, could not recall any similar improvement in well-being, brought about by the consumption of an element, in which that element had not been shown to be essential.

Exeter. JEFFREY FLETCHER.

HYPERBILIRUBINÆMIA IN PREMATURE INFANTS

SIR,—In the paper by Dr. Corner and her colleagues (April 2) it is stated that "Clinically, synkavit and 'Sulfasoxazole' have also been associated with hyperbilirubinæmia, and the inference is that these drugs interfere with bilirubin conjugation".

The role of synkavit in the production of neonatal hyperbilirubinæmia is not in dispute although the mechanism is not entirely clear. However it would be of interest to know what evidence, clinical or otherwise, implicates the sulphonamides in the production of hyperbilirubinæmia or interference with bilirubin conjugation.

The cases of kernicterus in newborn infants receiving sulphonamides were not associated with supranormal levels of serum-bilirubin.[5] The kernicterogenic property of the sulphonamides is due to displacement of bilirubin from the bilirubin-albumen complex in the blood [6] and possibly to an alteration in the permeability of the blood-brain barrier.[7]

It is of critical importance to realise that newborn infants on sulphonamides may get kernicterus at blood levels of bilirubin believed to be harmless and that intense jaundice is not to be expected.

Department of Child Health,
Royal Hospital for Sick Children,
Bristol. THOMAS E. OPPÉ.

AN EASIER ALPHABET

SIR,—May I thank Dr. Thomas for his kind remarks (April 9) and interesting discussion on redundancy?

As speech has developed through the ages 50% redundancy may represent a compromise between the speaker's haste and the recipient's incompetence. If 50% is adequate for speech there is no need for 2500% in our written language, especially as the rate of information intake is entirely under control of the reader. Illiterate people could be helped by increasing redundancy only if the extra information increased the differences between the letters, and even then it is doubtful. One could design an alphabet in which every letter differed from its fellow by two, three, or more units of information, but at each step the letters become more complex. An illiterate might find them more difficult, rather than easier, although the differences were greater. Roman numerals have a higher redundancy than Arabic yet illiterates do not find them easier—in fact, the easier Arabic, which were introduced some six hundred years ago, have almost replaced the more difficult Roman. If an object has many characteristic features it is usually identified by the most conspicuous and there the process ends. There is little point in examining the object again and reidentifying it by a second feature, much less a third or fourth unit of information.

To increase redundancy without increasing the differences between letters, by adding curls, balls, and spikes to every letter delays the writer, confuses the reader, and helps no-one. This is the useless type of redundancy present in our written language which makes illiterates out of many who can talk fluently and understand the spoken word without difficulty.

Whittingham Hospital,
Goosnargh, near Preston. S. L. PUGMIRE.

SIR,—The word "redundancy" when applied to written language can have at least two quite distinct meanings. When Dr. Thomas says that "it is an accepted principle of communication theory that redundancy serves to protect against errors in transmission" this is true only of redundancy in the design of the signal units, in this case the individual letters of the alphabet. For instance, the letter y must have a tail to distinguish it from the letter v, and though a tail three times as long might be thought redundant it would certainly make distinction that much easier, and consequently reduce any "errors in transmission" between page and perception.

In practice the degree of redundancy in letter design affects efficiency of communication much less than does redundancy in the *use* of letters. To use the letters ugh to represent the sound f in the word "cough" cannot by any stretch of logic or imagination be said to "protect against errors in transmission". It is this form of redundancy with which Dr. Pugmire is chiefly concerned, and his experiments with coloured cards of different shapes show that the inclusion of irrelevant information only makes reception of the message more difficult.

When Dr. Thomas says that a case might be made out for designing a language with high redundancy this could only be so if illiterates' difficulty lay in distinguishing individual letters. The inclusion of redundant letters could no more improve recognition of written symbols than could a compact

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6. Odell, G. B. *J. clin. Invest.* 1959, **38**, 823.
7. Johnson, L., Day, R. *Amer. J. Dis. Child.* 1957, **94**, 441.

script cause the increase in illiteracy which Dr. Thomas fears. To write "committee" instead of "comity" helps no-one—not even that stupid listener to whom one has to say the same thing over and over again.

Lee-on-Solent. A. S. JARRETT.

THE MEDICAL SERVICE COMMITTEES

SIR,—The tragic thing about the disciplinary tribunals is that they need to exist at all. However, what are a family to do when they discover their G.P. is lazy and incompetent? At first they will decide to change their doctor. Having found their E.C.4, they see they need to obtain the consent of the doctor they wish to leave in order to transfer. They may not wish to do this, for obvious reasons. If they do not wish to move house, the only alternative is for them to write to the executive council, who will effect a transfer after 14 days.

In the meantime granny is dying of pneumonia, and in desperation a relative calls on Dr. D down the road. Naturally, he feels diffident about accepting a colleague's patient under the circumstances, and this innocent feeling may be misinterpreted by the relative who thinks the local doctors are ganging up against him. In a fit of pique he lodges a complaint.

Those of us who want the capitation system abandoned have always recognised this muddle as one of its greatest faults. Capitation medicine must necessarily be static—doctors having "lists", and patients "belonging"; sometimes to their detriment. Dr. Wheatley (April 16) should actively support some more competitive and efficient system of medicine instead of trying to get at the executive council. Unfortunately your solution, Sir, is no better. How can an advocate protect his client when hearsay is admitted, and the rules of evidence are ignored? How can a chairman exercise proper control if procedure may be arbitrary?

Worthing. RICHARD H. DAVISON.

PALLIATION IN MALIGNANT STRICTURE OF THE ŒSOPHAGUS

SIR,—Mr. Moghissi's article (March 26), recommending the use of the Mousseau-Barbin tube in the palliation of œsophageal stricture, prompts us to report our less fortunate experience in two recent cases.

Our first patient was a woman of 75, admitted with almost total dysphagia from an inoperable carcinoma of the lower third of the œsophagus. A Mousseau-Barbin tube was inserted, but it became dislodged upwards during the first 24 hours by postoperative vomiting so that its lower end lay embedded in tumour tissue. Dysphagia was not relieved and the patient died 3 weeks later. At postmortem examination, the expanded bell of the tube was found to have produced a deep annular pressure ulcer, which had eroded through the œsophagus producing a deep groove on the aorta. It was apparent that had she survived a few weeks longer, the aorta would also have been penetrated.

The second patient was a man of 82 with a simple stricture of the lower œsophagus. When the stricture could no longer be dilated with œsophageal bougies, a Souttar's tube was inserted at open operation, and gave complete and painless relief for a period of 3 months; at this time the tube slipped through the stricture, and dysphagia soon recurred. A Mousseau-Barbin tube was inserted, and although the patient's dysphagia was relieved he complained of persistent severe pain girdling the lower chest from the early postoperative period until his sudden death from hæmorrhage 22 weeks later. Postmortem examination showed that the bell of the tube had eroded not only the œsophagus but also the aorta, producing the terminal catastrophic hæmorrhage. In addition, the lower end of the tube had produced a deep ulcer of the lesser curvature of the stomach.

The Mousseau-Barbin tube has the great advantage of relative ease of insertion, but our very limited experience suggests that the present design in 'Neoplex' is too rigid for safety, and would be better replaced by a more resilient material, better able to absorb the repeated trauma of aortic pulsations.

Vale of Leven Hospital, Alexandria, Dunbartonshire. R. A. JAMIESON
EWAN CAMERON
RONALD G. CLARK.

LUNG CANCER AND TOBACCO MOSAIC VIRUS

SIR,—I am glad to note that in his comment (March 26) on my letter, Mr. Pirie acknowledges the need for investigation of the possible relationship between tobacco mosaic virus (T.M.V.) and lung cancer and that he has gone so far as to suggest a way in which this may be done.

His analogy of the effect of a temperature gradient on the cellular R.N.A. of grilled steak does not appear to be relevant, unless he considers that all R.N.A.s are equal, in spite of the generally held view that some must be more equal than others! Surely the specificity of large molecules [1] does imply considerable differences between the R.N.A.s from various species, and surely it is the code carried by these molecules which is important rather than the presence of entirely different components in some R.N.A.s compared with others. Mr. Pirie has put this matter as clearly as anyone: "We do not know how similar the component parts of a virus are to normal components of the host; they may even be identical but differently arranged." [2]

His analogy of grilled steak is in fact somewhat unfortunate and it would have been more appropriate to compare the effect of heat on frying tomatoes, as these might at least contain a plant-viral nucleic acid which might well be T.M.V. R.N.A. It would also have the advantage that fried foods have been associated with the production of gastric cancer.[3] However, as it is most unlikely that either the steak or the tomatoes would be cooked in tobacco, the uniqueness of the temperature gradient and the processes surrounding it remains a fact for T.M.V. (and other plant viruses) in the cigarette.

The two a-priori requirements which Mr. Pirie cites are volatility for the nucleic acid and a special component in the R.N.A. of T.M.V. which is not found in other kinds of R.N.A. So far as volatility is concerned, I referred to the difficulty of seeing how the whole virus could pass over in tobacco smoke in view of its high molecular weight. If, however, ingestion rather than inhalation is important, then the question of volatility does not apply. Additionally, it would be necessary to consider whether nucleotides and nucleotide complexes derived from the R.N.A. might not in fact be carried over in the smoke. Neither does the a-priori postulation of a special component in the R.N.A. of T.M.V. appear to be required. The specificity of nucleic-acid molecules is not due to their possession of special components but almost certainly to the way in which these components are arranged and to the information code which they thereby convey. Small differences between normal and abnormal hæmoglobin [4] accentuate how small these changes may be to have wide implications, and the present conception of D.N.A. as a transmitter of hereditary information would be invalid without them. The conditions which surround viral R.N.A. near the burning end of the cigarette provide conditions in which analogue substitution can readily be envisaged in the R.N.A. or in its nucleotides. Also according to Reddi [5] the composition of T.M.V. R.N.A. is in fact different from the R.N.A. in the healthy leaf in that the uracil content of the virus was

1. Pauling, L. *in* Significant Trends in Medical Research; p. 3. Ciba Foundation Symposium, 1959.
2. Pirie, N. W. Proceedings of 4th International Congress of Biochemistry; p. 239. Vienna, 1958.
3. Stocks, P. British Empire Cancer Campaign Annual Report; p. 123. London, 1957.
4. Theorell, H. *in* Significant Trends in Medical Research; p. 18. Ciba Foundation Symposium, 1959.
5. Reddi, K. K. *Biochim. biophys. acta*, 1956, **23**, 209.

found to be about twice that in the plant R.N.A., so that there is also a difference here, contrary to Mr. Pirie's view.

It is possible that the products of combustion of tobacco contained in tobacco smoke could pave the way for other carcinogenic agents, exogenous or endogenous. The evidence relating to the evocatory effects of nucleic acids and their breakdown products [6] should constitute reasonable grounds for investigating the role of the viral T.M.V. nucleic acid. Since so little is really known about the effect of cocarcinogens and other substances on the structure of R.N.A. and since even less would appear to be known about the relationship of R.N.A. to neoplasia, work to exclude a possible relationship is desirable.

Opinions about improbability and the postulation of a-priori requirements are highly unsafe in a field where so much is unknown. One investigation would be better than a thousand opinions and comments.

Department of Public Health,
Bristol. P. W. BOTHWELL.

CORPORAL PUNISHMENT

SIR,—Although apparently shocked by Dr. Waycott's statement (March 26) that there is no proof of the deterrent effect of corporal punishment, Dr. Webster (April 2) gives no fact more relevant than the work of Pavlov.

The waters of psychology are deep and treacherous, but there are one or two points worth consideration. The "teddy-boy" outlook includes a masochistic element, seen in the curious attitude to the carcinogenic aspects of smoking: the smoker is now a hero facing martyrdom, looked on with awe by his schoolfellows. Likewise the birched boy became a hero.

More disturbing still is the undoubted connection between corporal punishment and sexual stimulation: the Marquis de Sade was not altogether a fraud. Dr. Webster might do worse than read certain passages in *Mr. Norris Changes Trains* or *Brave New World*.

Summerfield Hospital,
Birmingham. ROBERT J. HETHERINGTON.

IRON-DEFICIENCY ANÆMIA IN THE TROPICS

SIR,—Your issue of Nov. 14, passed on to me by a friend, is just to hand in the interior of the Bornean jungle. You comment (p. 831) on the W.H.O. report on the anæmia which is such a problem in the tropics.

While I agree that vitamin B_{12}, &c., is not necessary and that ferrous sulphate works wonders, I would suggest we should simplify the therapy. In my experience it is definitely better to avoid using "pills", for, of course, this leads to thousands of sufferers with a continual dependence on "pills" and more particularly the middle man who seldom hesitates to exploit his "wonder-working wares" amongst the poor interior peoples whom we doctors may have encouraged into this dependence.

In one community of North Borneo Muruts with whom I lived I found a striking anæmia in a high proportion of the people and a very severe anæmia in many of the women. By insisting on the eating of vegetables three times a day and drawing the whole community's attention to the situation we were able to transform the position. The long-term result has meant the virtual elimination of anæmia without a single pill being consumed. The community is also serving as an example to others who have no hope of meeting a doctor in the remoteness of the Bornean jungle.

Besides the usual ætiological factors in the sex-distribution there is an additional local factor. In animism as practised by the Muruts there are severe taboos on the eating of green vegetables by pregnant and lactating women—this in a community where lactation goes on for years rather than months, and where vegetables are normally only eaten when no fish or meat is available from the jungle.

Thus the problem is much greater than dietetics. Only those who have not lived with animism would ever belittle its fantastic power. The doctor who can introduce the tribesmen to a more powerful Person (*Luke*, 11, 20–22) is able to make particular contribution.

Looking back home from our experience in Borneo, it would seem that perhaps we spend too much time thinking of iron preparations and the relative frequency of the gastrointestinal disturbances when we should be thinking of diet.

Borneo Evangelical Mission,
Lawas, Sarawak, via Labuan,
Borneo. W. C. LEES.

CHILDREN IN POINTED SHOES

SIR,—Mr. Thomas' reference (April 2) to an article on Chinese feet in Hong Kong could, perhaps, be amplified.

In China proper, in the immediate post-war years, the professional classes alone wore leather shoes, possibly of Japanese origin, and one and all showed evidence of hallux valgus. The shoes were round-toed, low-heeled lacing shoes of relatively broad width, with a toecap, identical for men and women. Most coolie women over the age of thirty had bound feet, immediately identifiable in their blue or black cotton shoes because of their tiny, pointed wedge-shape coming sharply up into the "instep" with, obviously, no use of the toes or tarsal joints, including the subastragaloid, and no flexion or extension at the ankle. They stumped about as if on stilts and were terrifying in traffic as they plunged into it head down and scuttled across the street, looking neither to left nor right, arriving more often than one would have thought humanly possible.

Only once in the course of wide cross-country travels and examining large numbers of women and children was I able to get a bound foot exposed. Chinese colleagues had not thought this possible, but I managed it under the plea of examining after treatment for scabies, in which one insisted all the family sharing a bed should be treated with the affected children. In this instance the entire foot was turned under so that the woman walked on some part of the dorsum and somewhere underneath there was a clutter of toes covered in callosities. It was an obscene sight, but the patient regarded me indifferently as I looked at it. I have one X-ray of another bound foot, again obtained with difficulty through an orthopædic department: it was at that time a rare possession. The evidences round one showed clearly the amount of contortion infant bones will stand and explained in some part, for me, the lack of pain in toddlers' feet pushed into shoes much smaller than their feet, which used to be common enough in this country.

The footwear of the younger Chinese peasant or coolie woman and of many men in towns was the reasonably shaped, often home-made stuff shoe, but everywhere one also saw men barefoot or in sandals. The latter, made of straw, were constantly seen discarded—singly—on country paths and city pavements alike, as if it were too much trouble in passing to pick up a dropped shoe. These sometimes had pointed fronts barely covering the toes, sometimes a thong between first and second toes. The bare Chinese foot had a free hallux whose work could be well seen in the rickshaw-runner. I never, repeat *never*, saw hallux valgus in these people: I sometimes saw an enlarged first metatarsal head, for obvious reasons. The coolies dragging lorries (there were practically no motor engines) or carrying loads across their shoulders frequently bore enormous weights. One could quite often see a lad delivering ten *wooden* suitcases, slung five deep at either end of his shoulder pole, in a shopping area: wardrobes or pairs of chests-of-drawers on a man's back were common. Children I examined round the age of seven or eight frequently exhibited markedly pronated feet with knock-knee, features not met with in the younger age-groups. I attributed this to their starting to carry coal or nightsoil, again in buckets slung doubly from their shoulder poles, at this tender age: a male colleague tried in vain to lift

6. Davidson, J. N. The Biochemistry of the Nucleic Acids; p. 214. London, 1957.

by hand what one girl-child hitched on to her shoulder without too much difficulty. No age, once the child had walked (they walked very late), was too young to work in China.

An extraordinary thing was the unwillingness of the very young of either sex to bare their feet (in towns they mostly wore the stuff shoe). They stripped willingly and almost uninvited as their turn approached for medical examination and let one pummel and sound them, look at their throats, and evert their eyelids (looking for the ubiquitous trachoma) without the slightest qualm, but hesitated and silently resisted till the last ditch when asked to remove their shoes. Little babies often had the gayest tigers embroidered on their shoe-soles: did their elder brothers and sisters think of evil spirits approaching through the foot-soles too?

London, S.W.1. MARGARET EMSLIE.

TREATMENT OF FÆCAL INCONTINENCE

SIR,—Fæcal incontinence is a common and difficult condition in geriatric practice. There are two main causes: fæcal impaction, when the hardened rounded scybala act both as an irritant and a ball-valve allowing only fluid fæces to pass; and impaired nervous control of the defæcation reflex, due to cerebral arteriosclerosis or brain damage due to cerebrovascular accidents. The patient with hemiparesis often regains the ability to walk, but tends to remain in hospital because of the difficulties of home care of an incontinent patient.

Recently we have been treating these patients with neurogenic incompetence by imposing periodicity of bowel action by alternate use of agents with opposite pharmacological effects, in this case mist. kaolin et morph. and standardised senna (' Senokot ') given at 12-hourly intervals.

The opiate, by interfering with the propulsive movements of the small and large intestines, leads to more complete absorption of water from the fæces and at the same time the tone of the external sphincter is greatly enhanced.[1] The active glycosides of senokot, on the other hand, are absorbed from the small intestine, re-excreted in the colon, and after activation by bacterial flora they stimulate the parasympathetic nerves of Auerbach's plexus. This results in the reproduction of the physiological process of defæcation without any evidence of irritation of the bowel mucosa.[2] By regulating the dose of the opiate mixture and the senokot, control over bowel action can be achieved. The results have been encouraging, as the following show:

CASE 1.—A woman of 74. Since a left hemiparesis in April, 1959, she remained in hospital, chiefly because of continued fæcal incontinence. Mist. kaolin et morph. 15 ml. o.m. and senokot tabs. 1 o.n. were started in August, with complete control of the incontinence. She was discharged from hospital in October, 1959, and has remained well since.

CASE 2.—A woman of 86. Already suffering from advanced cerebral arteriosclerosis, she was admitted in April, 1959, with a fractured neck of femur. During her three-month stay in the orthopædic ward she was continuously incontinent of fæces. Since starting mist. kaolin et morph. 15 ml. o.m. and senokot tabs. 1 o.n. in July she has remained continent.

CASE 3.—A man of 71. He was admitted after a severe right hemiplegia with total aphasia and double incontinence. Two weeks after admission mist. kaolin et morph. 15 ml. o.m. and senokot tabs. 2 o.n. were started and he remained continent until his death from pulmonary embolism three months later.

CASE 4.—A woman of 70 suffering from advanced cerebral arteriosclerosis with many bilateral thrombotic episodes. When given mist. kaolin et morph. 15 ml. in the morning and senokot tabs. 1 at night she continued to have nocturnal incontinence, but on reversing the order of the drugs, this disappeared.

CASE 5.—A woman of 78. She was incontinent of fæces following a right hemiparesis two months ago. As with case 4 she continued to have nocturnal incontinence when the drugs were given in the usual order, but since being given senokot tabs. 1 in the morning and mist. kaolin et morph. 15 ml. at night she has remained continent.

Provided that fæcal impaction is always excluded by careful digital examination, this regime seems to have considerable value in the management of elderly patients with fæcal incontinence.

Whittington Hospital, Highgate Wing, London, N.19. A. S. JARRETT
A. N. EXTON-SMITH.

1. Goodman, L. S., Gilman, A. The Pharmacological Basis of Therapeutics; p. 229. New York, 1958.
2. Fairbairn, J. W. *Brit. med. J.* 1958, i, 218.

PERTHES' DISEASE

SIR,—Professor Trueta in his rejoinder (April 2) to the letter by Dr. Palmer and myself (in which we stated that we not infrequently saw cases of Perthes' disease) cited various references about this condition in Negro subjects. The works quoted came from the Southern States of the United States of America and Argentina. It is certainly of interest to note that in these areas people of Negro origin do not appear to suffer from Perthes'. However, in contrast, the condition is not unduly rare in Western Nigeria, Northern Nigeria, Ghana, Jamaica, and Southern Rhodesia. I base this statement on personal experience and discussion with orthopædic surgeons and other radiologists practising in these areas. The statistical figures culled by Professor Trueta are from the Negro populations originating from the Congo basin, whereas the Nigerian, Ghanaian, and West Indian (Jamaica) are from the Guinea Coast. It may well be that this difference in geographical origin is also reflected in a genetic factor that may protect some individuals from the ravages of Perthes' disease.

I feel that Perthes' disease is as common here as in Europe, though of course it is very difficult to base any statistics on hospital experience, which may not reflect the pattern of the population as a whole.

University College Hospital, Ibadan, Nigeria. W. P. COCKSHOTT.

SIR,—I should like to disagree with Professor Trueta in his statement that " the Negro child appears to be immune to Perthes' ". I have seen Dr. Cockshott's cases and have 9 of my own with normal hæmoglobin studies and followed through the development and resolution of the condition.[1]

This seem to be yet another instance where one cannot say a condition never occurs in a particular race but merely shows a reduced incidence.

University College of the West Indies, Mona St. Andrew, Jamaica. J. S. R. GOLDING.

PSYCHIATRIC DAY HOSPITALS

SIR,—The letter of April 9 from Dr. Richard Fox and his colleagues should be generally welcomed, firstly for adding information on a subject in which it is inadequate, and secondly for its emphasis on the need for further research. However, they have perhaps taken a rather over-cautious approach—for instance, in their limit of a half-hour's journey to the day hospital. Many day patients have a considerably longer journey than this and make it willingly, in order to obtain treatment without the necessity for admission. Is it also neccessary to insist that patients are unable to carry on their normal lives before offering them the benefits of day-hospital treatment?

In our present situation, with psychiatric facilities so generally inadequate, a day hospital can only become inactive if it is in the wrong place or if it has failed to establish links with the community around, so that they are unaware of its existence or function. If " strategically " placed, they should be

1. *J. Bone Jt Surg.* 1959, **41B**, 4.

adequately served by public transport; special hospital transport would add very considerably to the expense.

Whilst it is true that we have little definite information on the cost per patient-illness of day patients as against inpatients, there can be no doubt that as far as capital cost is concerned, there is an immense advantage in day hospitals. They can readily be converted out of existing buildings or can be accommodated in relatively cheap temporary structures. In the present state of uncertainty as to the future arrangement of psychiatric services, they can therefore provide a great deal of treatment, without much capital commitment. If experience from the first few years working of the Mental Health Act should prove that, in fact, other kinds of hospital provision were more suitable, these buildings could then be scrapped with very little loss. Inpatient units must inevitably require capital expenditure on a much greater scale, causing rigidity in planning, in the same way that 19th-century mental hospitals do today. This aspect of the question is discussed in the report by Farndale which is shortly to be published, and which is likely to supply much ammnution for these controversies.

Littlemore Hospital,
Oxford H. L. FREEMAN.

REINFORCEMENT OF IMMUNITY TO DIPHTHERIA

SIR,—In a symposium [1] on immunisation in childhood two speakers advocated the use of toxoid-antitoxin floccules (T.A.F.) to reinforce immunity against diphtheria. I was somewhat surprised to see no mention of another floccule antigen, alkali-dissolved floccules (D.F.), which has been used with satisfaction in South Africa for 10 years.

It is employed as the secondary stimulus in those people who have received $AlPO_4$—adsorbed floccules (A.D.F.) as a primary stimulus, and as a booster in older children, adolescents, and adults.

D.F. and T.A.F. are tolerated by the body to the same extent, but D.F. has certain advantages. It is more easily prepared, is more antigenic, is water clear, its toxoid content can be found by the flocculation test, and it contains much less protein of equine origin.

Either the publications [2–4] referring to A.D.F. and D.F. have escaped the notice of the British authorities or, as concerns the use of D.F. as a reinforcing injection, they have found disadvantages of which we in South Africa are unaware. It would be interesting to have their views.

Germiston,
Transvaal. P. B. PEACOCK.

CHEMOTHERAPY OF MYELOMA AND MULTIPLE MYELOMA

SIR,—Do myeloma and multiple myeloma respond differently to chemotherapy? Descriptions of the chemotherapeutic control of both diseases indicate little difference in the responses.

Nabarro [5] noted no response in a patient with multiple myeloma who was given the nitrogen mustard, HN2, and no benefit was observed in another patient with myeloma given the aromatic mustard, R48. Marchal et al.[6] reported clinical remissions in 3 out of 4 patients with myeloma, following treatment with corticotrophin (A.C.T.H.) and cortisone, and a slight response in 1 patient with multiple myeloma on the same therapy. Fadda et al.[7] described remissions of 6 to 24 months in a case of myeloma and several cases of multiple myeloma given urethane, corticotrophin, cortisone, and radiotherapy.

A comparison, however, of the results of treating 485 patients with multiple myeloma with a group of patients described by 30 other investigators as having myeloma reveals some interesting differences in response to chemotherapy.[8] Some of these differences are as follows:

Chemicals	Multiple myeloma		Myeloma	
	No. of cases	No. of remissions	No. of cases	No. of remissions
Urethane	222	160	1	1
A.C.T.H./cortisone	64	31	19	9
Stilbenes	41	17	31	26
Tretamine	36	6	5	3
N-mustards	30	20	11	9
Radiophosphorus ..	17	7	35	14

Diamond [9] and others have pointed out the difficulty of recognising clinically solitary plasmocytoma, and undoubtedly a number of the cases of myeloma described in the literature are disseminated plasma-cell myelomas or multiple myelomas. There is need for more controlled studies on the response of these malignant diseases to chemotherapeutic agents before it can be declared that a difference does exist.

Furman University,
Greenville, South Carolina. JOHN R. SAMPEY.

HYPERCALCIURIA IN WILSON'S DISEASE (HEPATICOLENTICULAR DEGENERATION)

SIR,—In 1959 we reported hypercalciuria in 4 of 5 patients with Wilson's disease.[10] Of the 4 patients, 1 had bilateral nephrocalcinosis and another had a calculus in the left kidney.

We have since had the opportunity to study another patient with Wilson's disease who had hypercalciuria, thus confirming our original observation.

A 27-year-old white man with œdema and jaundice was first seen at the Mayo Clinic in July, 1959. In 1956 he had noted some enlargement of his breasts. He felt well otherwise until the middle of 1958 when he began to tire easily and to gain weight. In May, 1959, he became jaundiced and was found to have œdema of his legs and ascites. About that time he first noted a tremor of his hands. That same month he was admitted to the hospital and found to have impending hepatic coma. His condition improved and he was dismissed from the hospital the next month. After he returned home, however, his condition worsened and in July he registered at the clinic.

Physical examination revealed a slight static tremor of the hands and some slurring of speech. Typical Kayser-Fleischer rings were present as well as left pleural effusion, ascites, and œdema of the legs. The lower edge of the liver was palpable at the level of the umbilicus. The lower edge of the spleen was 4 fingerbreadths below the left costal margin.

Laboratory investigations.—Prothrombin-time, 37 sec.; concentration of bilirubin per 100 ml. serum, 0 direct and 2·74 mg. indirect; cholesterol-cephalin flocculation test, 4+; thymol turbidity 7 units; alkaline-phosphatase 15·6 King-Armstrong units, uric acid 1·7 mg., calcium 8·4 and 8·0 mg., and inorganic phosphate 3·3 mg. per 100 ml. serum; cholesterol 153 mg. per 100 ml. plasma; copper-oxidase activity present in the serum; total proteins, 4·94 g. per 100 ml. serum with electrophoretic fractions of 1·57 g. albumin, 0·26 g. alpha-1-globulin, 0·34 g. alpha-2-globulin, and 2·77 g. beta and gamma globulin combined.

X-rays of the thorax showed a large pleural effusion on the left side. The renal areas did not show evidence of nephrocalcinosis or renal calculus.

The daily urinary excretion of calcium and other materials was measured for three days during which time the patient was given a diet containing an average of 213 mg. of calcium, 2·93 mg. of copper, 62 g. of protein, 111 g. of fat, and 244 g. of carbohydrate per twenty-four hours and distilled water as desired. During this period, the urinary excretions of calcium were 317, 331, and 258 mg. (average 302 mg.) per twenty-four hours. Over the same three-day period the average urinary excretion of phosphorus was 829 mg., copper 0·23 mg., and alpha-amino-nitrogen 414 mg., all per twenty-four hours.

1. Proceedings of a Symposium on Immunisation in Childhood; pp. 75, 77. Edinburgh and London, 1959.
2. Mason, J. H. *J. Hyg. Camb.* 1950, **48**, 418.
3. Mason, J. H. *Lancet*, 1951, **1**, 504.
4. Mason, J. H., Robinson, M., Brown, M. S. *S. Afr. med. J.* 1953, **27**, 293.
5. Nabarro, J. D. N. *Brit. J. Radiol.* 1951, **24**, 507.
6. Marchal, G., Duhamel, G., Gervais, P., Toulouse, J. *Sem. Hôp., Paris*, 1954, **30**, 898.
7. Fadda, C. F., Lucchini, M. A., Vera, G. A. *Rev. méd. Valparaiso*, 1953, **6**, 370.
8. Sampey, J. R. *J. S. C. med. Ass.* 1959, **55**. 183.
9. Diamond, H. D. Medical Management of Cancer. New York, 1958.
10. Litin, R. B., Randall, R. V., Goldstein, N. P., Power, M. H., Diessner, G. R. *Amer. J. med. Sci.* 1959, **238**, 614.

With the diet used in this study, a value for urinary calcium in excess of 170 mg. per twenty-four hours is above normal. By this criterion, the patient had hypercalciuria.

It is not known whether the hypercalciuria in this patient and in our other 4 patients was caused primarily by increased absorption of calcium from the gastrointestinal tract, by a renal defect, or by a skeletal disease. The hypercalciuria was not associated with hypercalcæmia or known skeletal disease.

Additional study is necessary to determine the cause and frequency of hypercalciuria in Wilson's disease. Since it is well known that renal tubular dysfunction may be present in Wilson's disease, the hypercalciuria may represent another renal tubular defect.

RAYMOND V. RANDALL
NORMAN P. GOLDSTEIN
JOHN B. GROSS
MARSCHELLE H. POWER.

Mayo Clinic,
Rochester, Minnesota.

THE PERSONAL DOCTOR

SIR,—The review of the state of general practice here and in the U.S.A. by Dr. Fox is a most important contribution to the subject. It raises and stimulates much thought.

I am quite certain that there is much more to general practice today in Great Britain under the N.H.S. than just "personal doctoring", which is after all an essential technique of all good medical and surgical practice.

The clinical opportunities in general practice offer the doctor almost unlimited scope. Dr. Fox tends to assume, or that is the impression he gives me, that real and proper medicine can only be practised in the atmospheres of hospitals and clinics, and that all that is left the G.P. are a mass of trivia and the personal support and comfort of the individual patient. I find this not to be the case in my own practice, which must also be the experience of others.

In a survey of referrals in my practice I found that I was able to manage and care for almost 95% of the work in any year. Admittedly I have access to local X-ray and pathology departments, but the point I want to make is that there is no real need to think in terms of beds and clinics to be able to practise good general practice. In the same study [1] I showed that many serious diseases such as pneumonias, coronary occlusions, and anæmias do not need admission to hospital. This is general practice as I see it, looking after and coping with the vast majority of disease in my community. To it must be added an appreciation of natural history of disease in a longitudinal sense, the appreciation of the patient as an individual, of the influences of environment and social factors.

As for the G.P. getting back into the hospitals and having G.P. beds in which to treat his own patients, I personally am still not convinced that this is necessary to improve standards. I wonder how many G.P.s *really* want this. Facilities for investigating one's own patients, yes, but when I have done all I can at home, with help of the district nurse, there is little else that I, as a G.P., would be able to do if I was looking after that same patient in a hospital bed. When I refer a patient for admission I feel that the patient requires the full facilities of the hospital set-up, with housemen and consultants playing their part. I certainly could not be on 24-hour call to care for my patients in hospital and to put up drips and carry out other emergency procedures as well as look after my practice, and I think it would be bad in principle to expect the houseman to take orders from me as well as his consultant chief. What is required now before further action is taken on this important matter is to carry out a realistic review of what goes on in G.P. hospitals at present, just as Forsyth and Logan have done in Barrow on other hospitals [2] and see precisely what types of cases are being treated in these hospitals and why.

Dr. Fox has not convinced me that drastic changes are required in British general practice. The basic principles of personal and family doctoring plus general medical care for 95% of the illnesses of the community seem to me to be potentially the best in the world. What we do need is to see how improvements can be made in the existing type of practice. To do this we need to define the faults and the problems still more clearly and more simply and then to devise and try possible remedies.

The last few words of Dr. Fox's essay are most important: "let us adopt—or rather resume—their excellent habit of wide experiment".

Beckenham, Kent. JOHN FRY.

SIR,—Like Dr. John Hunt (April 9), I should like to take issue with Dr. Fox on this notion of the "extinct general practitioner.' It may be true of the urban species, of whom I am not qualified to speak: it is certainly not true of the rural, who has as much honest doctoring to do as ever in the past three decades and has, increasingly, to bully and badger his consultant friends into doing, or getting done, what needs to be done for those of his patients who require hospital services.

I should like to know more of the functions envisaged by Dr. Fox for the "personal" doctor, who sounds to me less of a doctor than a sort of medical curate; one who visits, exchanges ideas, throws out suggestions, but, in fact, accomplishes precisely nothing of therapeutic value.

Dr. Fox stresses the importance of time spent on the sick man and, of course, he is right—when the man is really sick. But if he—or, more often, she—is merely bellyaching about trivialia he should, for the good of his soul, be kindly but firmly dealt with and speedily dismissed.

It is here that the G.P. who speaks as one having authority can do something to alleviate the panics produced by publicity and discourage that morbid and humourless preoccupation with health which is now the bane of mankind.

Crediton, Devon. L. N. JACKSON.

*** Dr. Fox writes: "The length of my article must have obscured my meaning. I want the personal doctor to practise the same kind of responsible and skilful medicine as Dr. Jackson and Dr. Fry."—ED. L.

SIR,—We must be grateful to Dr. Fox for his account of the current practices in the U.S.A. We are sure that all will see from this the inherent dangers of "impersonal doctoring".

As an adjective "personal" must refer to any medical man worthy of the name doctor, irrespective of whether he be general practitioner or specialist. It is not the prerogative of either one alone to administer "T.L.C.". Where the general practitioner has the advantage over the specialist, and always will have, is in that the former maintains daily contact with every department of medicine, and the latter does not. Consequently, as the number of true consultants diminish, and they are replaced by highly trained specialists, he is the principal remaining source of a balanced medical knowledge and opinion. The latter is much prized by the patient, who is often in doubt about advice proffered by the specialist.

The specialist, on the other hand, remains particularly competent in his own department, but his knowledge and experience outside of it becomes progessively more vestigial. This, we would suggest, makes him the person least able to

1. Fry, J. *Brit. med. J.* 1959, ii.

2. Forsyth, G., Logan, R. F. L. Demand for Medical Care. Nuffield Provincial Hospitals Trust, 1960. See *Lancet*, April 16, 1960, p. 871.

assess the competence of colleagues in other fields, and what their limitations should be, whether general practitioner or specialist.

If there are to be any restrictions on practice, they should be clearly defined, at the time of registration, by the G.M.C. Thereafter, a doctor's practice should depend entirely on his ability to build a reputation for himself in his selected specialty, one of which is general practice. No person, or persons in whatever guise, or for whatever end, should be allowed to restrict a practitioner arbitarily in his selected field, unless negligent practice can be demonstrated. In all specialties it must be left to the doctor to decide whether he thinks himself capable of managing a particular case or whether he needs help. We feel sure that consultants, and specialists of consultant rank, would be the first to resist a direction that they were not capable of handling certain cases in their own specialty.

Llantwit Major, Glamorgan. NORMAN R. SALES
PETER H. THOMAS.

SIR,—Dr. Fox, after studying the American medical scene, draws what I believe are wrong conclusions as to the future of general practice in this country. He rightly makes his point, that unless the family doctor is seen still to perform some important function for which independence is necessary he will eventually be absorbed into the hospital system. But thereafter Dr. Fox seeks to put back the clock by perpetuating the picture of the family physician practising from his own home or in partnership in the traditional way.

Under the National Health Scheme, with the State paying the bill, the relationship is no longer between doctor and patient but is now between doctor, State, and patient. The community expects the profession to practise efficiently, and however personal our predecessors were in their attentions they could never be described as efficient in terms of modern preventive medicine as measured by mortality and morbidity rates.

The modern general practitioner cannot practise efficiently on his own from his own home. He is a member of a team—a team with ancillary helpers all skilled in their own profession—and the closer the team works the better.

General practice must evolve into group practice or health-centre practice where, with nurses, secretaries, laboratory aids, and health visitors, the family doctor can fully utilise the modern means of preventive medicine.

Dr. Fox, like Canute of old, seeks to hold back the tide.

Darbishire House Health Centre, Manchester. H. W. ASHWORTH.

Parliament

Royal Commission's Recommendations Accepted

IN a written answer on April 11, Mr. DEREK WALKER-SMITH, the Minister of Health, announced that the Government were prepared to accept as a whole the recommendations of the Royal Commission on Medical and Dental Remuneration, provided that the doctors and dentists were ready to accept them on the same basis. Representatives of the professions had been informed. Mr. Walker-Smith said:

We have drawn attention to various matters which are an integral part of full acceptance of the recommendations, including the establishment of a standing body to keep medical and dental remuneration under review on the lines proposed by the Commission. For a number of reasons, however, it is not possible to adopt the Commission's proposal that the Inland Revenue should furnish the review body with comprehensive information about professional earnings generally, but the Government are confident that the review body will be able to obtain the necessary information by other means, such as sample inquiries, and will of course be ready to give the body any help to this end that lies within their power.

The preliminary discussions we have had with representatives of the professions have been helpful and we have been able to clarify a number of points. We have offered as the next step to arrange for the proposals to be worked out in detail jointly by officers of our departments with representatives of the professions in order that as clear and comprehensive a picture as possible of their practical effect may be put before their members. We understand, however, that before this offer to engage in detailed discussions can be accepted it will need to be put to the professions through their appropriate channels. It is our hope that the professions will reach their decisions, and that discussions will begin, as soon as possible.

It is estimated that the extra annual cost falling on the Exchequer if the proposals are agreed will be about £11½ million net. The extra cost which would fall in 1960–61 is, however, estimated at £41½ million net, because the payments recommended by the Commission in that year and because of other temporary features.

The council of the British Medical Association have announced that they will recommend the special representative meeting on May 19 to accept the Minister's offer and his invitation "to enter into detailed discussions by means of joint working parties".

Training of Nurses

On March 13 Mr. KENNETH ROBINSON prayed against a Statutory Instrument which would permit the reintroduction of a minimum educational standard for entry into most parts of the nursing profession,[1] because, despite the General Nursing Council's wish that the change should apply to all parts of the nursing profession, the Minister had excluded mental nurses. This decision would perpetuate old prejudices and seemed to support the idea of a two-class nursing system. It was no secret that the Minister and his advisers had disregarded the Council's advice because, despite recent improvements, recruitment to mental nursing was still far from adequate. It would be a disaster to erect an educational barrier which might exclude many potential recruits who would ultimately make admirable nurses. There were many excellent mental nurses—and, Mr. Robinson believed, general nurses, too—who had the right sort of temperament, the energy, the understanding, and the intelligence to do the nurse's job admirably, but who lacked the educational qualifications, and perhaps even the kind of aptitude needed to obtain them. He agreed with the Minister's reasons for excluding mental nurses. It would be highly dangerous to limit in any way the intake of mental nursing students. But the status and prestige of the mental nurse within the profession would be further damaged by this new distinction, and this would have a detrimental effect on recruitment. In the circumstances he suggested that it was wrong to introduce an educational standard, at any rate at present, even in general nursing. He believed that it would have a serious effect on recruitment there, too. In the London teaching hospitals there was no recruitment problem, but the hospitals of the industrial areas of the North were forced, if they were to have any student nurses, to take nearly all comers who showed some aptitude for nursing. The avowed policy of the G.N.C. was to train more assistant nurses and fewer nurses. He feared that we might well be in danger of finding ourselves at the end of the day with a small highly trained elite and an inadequate rank and file to back it up. He had never believed that entry into any profession ought to be limited to those who could be expected or might be expected to reach the top.

Miss PITT replied that the Minister had consulted all the hospital authorities before approving the change, and it was generally felt that the reintroduction of a minimum educational

1. See *Lancet*, April 2, 1960, p. 761.

standard was desirable to cut down wastage. It was possible to make the change now because of the improvement in recruiting and the " bulge " of 18-year-olds. But the staffing situation in the psychiatric hospitals was not yet sufficiently established to make it right for the Minister to reach a decision, now, that the educational requirement should become compulsory in them on July 1, 1962, as it would in other hospitals. Where they were prepared to do so, it was open to psychiatric hospitals to apply the educational requirement to their student nurse entry straight away, and the Minister would be glad to see as many as possible do so. He intended to keep the matter under close review in the light of experience of the way in which the new educational standard worked in practice, including experience gained by psychiatric hospitals in applying the new standard on a voluntary basis, and a fresh assessment of the position in the psychiatric hospitals would not necessarily be postponed until after July 1, 1962.

Population (Statistics) Bill

At the report stage of this Bill on April 12 Mr. DEREK WALKER-SMITH, the Minister of Health, introduced a new clause which put on a statutory footing the reporting to Parliament of the statistics derived under the 1938 Act and the information about stillbirths as expanded by the present Bill. This expansion of the basis of statistical information and its reporting would help research and subsequent genetic evaluation. By recording the cause of death of stillbirths in England and Wales it was expected, he said, that about 3800 stillbirths and 3400 deaths after birth would be available each year for the study of congenital malformations. With the Scottish figures, this would give a total of about 8200 cases a year, which would be enough to allow the necessary research to be undertaken. With these figures, we might hope that in due time we should be able to determine the porportions and types of congenital abnormalities due to genetic defects. It would then be possible to investigate what factors were responsible for producing these genetic defects, and to find the proportion of cases due to the workings of genetic defects long present in the race, compared with those due to newly arisen genetic change.

The tables relating to the causes of stillbirth would be published in Part I of the Registrar General's *Annual Review*. In Part 3 of the review there would be a comment and explanation of the new information authorised in the Bill. The date for introducing the collection of information about stillbirths would be advanced to July 1.

Dr. EDITH SUMMERSKILL regretted that the new clause did not ask for a yearly report from the Medical Research Council or at least a full report in the Minister's annual review.

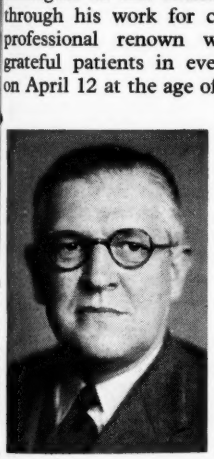
The Bill was read a third time.

Obituary

ARCHIBALD HECTOR McINDOE

Kt., C.B.E., M.B. N.Z., M.S., M.Sc. Minnesota, F.R.C.S., F.A.C.S.

WHEN the war began in 1939 Sir Archibald McIndoe's reputation was already firmly established among his colleagues in this country. By the time the war ended, through his work for casualties at East Grinstead, his professional renown was international and he had grateful patients in every part of the world. He died on April 12 at the age of 59.



Stoneman

He was born and educated in New Zealand, and graduated M.B. from the University of Otago in 1923. Almost at once he joined the staff of the Mayo Foundation at Rochester, where he worked with Charles and William Mayo and Counsellor. His seven years at the Mayo Clinic showed immense industry and promise, and he made important contributions to the pathology of the liver and the surgery of the biliary tract. In 1930 he decided to seek his fortune in England, and, under the compelling influence of Sir Harold Gillies, he turned his back on general surgery and took up the almost unrecognised specialty of plastic surgery. Hard work was always part of his nature. He had already acquired the degrees of M.SC. and M.S. from the University of Minnesota and the F.A.C.S., and he now quickly gained the English F.R.C.S. Within a short time he was appointed to the staff of St. Bartholomew's Hospital.

At that time there were only two other consultants who gave all their time to plastic surgery, and McIndoe seized the opportunity to develop the specialty, taking his full share both in technical advances and in the establishment of new policies. During the pre-war decade he published important papers on hypospadias, congenital absence of the vagina, mammaplasty, facial reconstruction after cancer, cleft lip, fractures of the mandible, lymphœdema, cartilage grafting, and the surgical treatment of X-ray burns. They all bore the hallmark of his capacity for hard work, his questing imagination, and his mastery of technique. It was at this phase of his career that the war came. A year earlier he had been made civilian consultant to the R.A.F., and he was at once appointed to the new E.M.S. unit for burns and maxillofacial injuries at East Grinstead as surgeon in charge.

A colleague, to whom we are indebted for much of this notice, adds the following personal tribute.

" Much has been written of McIndoe's work on burned airmen, and sometimes the subject has perhaps been treated with false emphasis. In fact it was a striking achievement; technically he mastered many problems—the massive grafting of burned eyelids, and the relief of hyperextension deformities of the hands, to name but two—while in the psychological and economic aspects of morale he was deeply perceptive. He had, and consciously developed, an exceptional knack for earning the confidence of young airmen, and he quickly came to terms of close friendship with many of them. Some were brilliant and tragic figures like Richard Hillary; some were ordinary youngsters with unexciting personalities and few gifts. Both types felt at ease with him.

" At the same time he knew how to persuade men occupying high positions in the direction of the war to provide facilities which he deemed essential to the treatment and (above all) to the rehabilitation of these burned and disfigured patients. Despite two serious operations during the war, he travelled extensively, and wherever he went brought not only invaluable clinical guidance but also that boundless optimism and energy which were his particular genius. After the war honours crowded in upon him, from Holland, Poland, Czechoslovakia, and France; and perhaps a knighthood in 1946 meant less to him than his vice-presidency of the Royal College of Surgeons. During the last fifteen years of his life, his enormous energies proved equal to a vast number of claims on his time; and in very recent days, tireless as ever, he was busy initiating a new department for research into problems of homografting.

" Yet all these activities—administrative, literary, and clinical—were but one side of a man of bustling and untiring energy. The immensely gifted surgeon turned easily to the cheerful company of his friends and his home. He was proud of his possessions and eager to enjoy them and share them. Believing that busy men should relax with energetic recreations, he was seldom happier than when pursuing big game in East Africa, whether with rifle or camera. Those who lived with him

on holiday have described a different person—still eager and acquisitive, but leisured and serene. There are few corners of the world that will not share this country's sadness in the loss of so gay, so dynamic, and so dedicated a man."

Of McIndoe's work for the Royal College of Surgeons J. P. R. writes:

"By his own exertions and enterprise he made for himself a place and a function in the college which it will be difficult if not impossible to fill. When he first joined the council he started, as everyone does, in a very quiet way, though it was noticeable from the outset how methodical he was with his paper work, and how punctilious in attending to the various duties allotted to him. He was rightly critical of the number and complexity of our committees, and during his term as vice-president an attempt was made to simplify the procedure of college business.

"His clear head and incisive speech made him an excellent committee man, and when he was in the chair the work went very smoothly and expeditiously because it had been well thought-out by him beforehand. He was not very interested in the academic side of college life and the consideration of the arrangements for courses of lectures and other forms of teaching frankly bored him, as did arguments about university routine and regulations.

"He had two major interests—the training of surgeons, and in particular the training of young plastic surgeons, for which purpose a special organisation was set up in the college to give advice to the Ministry of Health about the staffing of the centres for plastic surgery in England and Wales; and the financing of the college both for its reconstruction after the war and for its maintenance.

"He made a great success of his period of office as chairman of the finance committee, but undoubtedly his greatest contribution to the welfare of the college, the benefits of which will be enjoyed for many a long day if not 'for ever', was his attracting to the college laymen who were willing and soon became enthusiastic to further its scientific work, and who were able to give substantial and even princely donations to make the buildings grow and the work continue. McIndoe had a clear view of the ideals for which the college is striving, and he had the supreme gift of being able to fire other people, both professional and lay, with his own enthusiasm to join with him and his colleagues in the council in the pursuit of these ideals.

"Though it looked as though this sort of evangelistic endeavour came easy to him, in fact it cost him a very great deal in thought, in time, in concentrated effort to persuade a doubtful and hard-headed businessman that this was the best outlet for his charitable benefactions; in fact, in the end it cost him his life, for apart from his professional work at East Grinstead and in London he concentrated his whole energy, physical and mental, on working for the college. Little wonder that his colleagues cannot bring themselves to believe that he is gone! The least they can do in respect for his memory is to redouble their effort to finish the work he started so well and so nearly completed."

By his first marriage, which was dissolved, Sir Archibald had two daughters. In 1954 he married as his second wife Mrs. Constance Belcham, who survives him.

WILLIAM RODNEY FORRESTER-WOOD

M.A., M.B. Cantab., F.R.C.S.

Mr. W. R. Forrester-Wood, senior general surgeon in the Brighton and Lewes and Mid-Sussex hospital groups, died on April 6 at the age of 57.

His father was a general-practitioner surgeon in Southport. He originally wished to enter the Army, but the loss of sight in one eye at the age of 12 prevented this. He was educated at Cheltenham, Caius College, Cambridge, and St. Bartholomew's Hospital. After qualifying in 1929, he held house-appointments at Addenbrooke's Hospital, Brighton Infirmary, and the Royal Sussex County Hospital. He took the F.R.C.S. in 1932 and remained in Brighton in consulting practice. He was elected to the staff of the Royal Sussex County Hospital, and he was also appointed surgeon to the Royal Alexandra Children's Hospital in Brighton, and the Haywards Heath and other Sussex hospitals. He was on the hospital management committee of the Brighton and Lewes hospital group and for some years was the chairman of its medical and medical-staff committees.

W. A. B. writes:

"Forrester-Wood's special interest was children's surgery, but he took up thoracic surgery in the '30s and performed major operations in that specialty as a routine—with the exception of valvulotomy, which he consistently refused to undertake. He was in wide demand for private work over a large area, and his judgment, technical ability, and personality made him popular and trusted by doctors and patients alike. He was the unchallenged and universal choice as chairman of medical and medical-staff committees, for his colleagues had implicit trust in him, and his outwardly calm temperament, firmness, and humour controlled many difficult situations.

"His responsibilities were extensive and heavy, and in 1958 he had a myocardial infarction. He recovered reasonably and after a year returned to committee work, though no longer as chairman, and was still heavily relied on. But physical limitations returned, so that even his beloved fishing became a labour. The loss of this able and trusted man will be keenly felt, for he combined the values of the older generation with the judgment and abilities of the new."

Mr. Forrester-Wood leaves a widow and a son.

Dr. J. J. COULTHARD

Two friends add their tributes to the obituary of Dr. Coulthard which appeared last week.

"He was a man who gave his best at all times to anyone in trouble," writes D. L. B. "No-one worked harder or had higher standards. To him all men were equal".

H. W. S. W., a surgical colleague, says: "I learnt to regard him as one of the best general practitioners I have ever met. . . . His devotion to his patients was almost obsessive, but it was tempered with knowledge, insight, and rare judgment, a blend of qualities which gave him just the right degree of detachment without obscuring his interest and humanity. . . . He managed to get through his work by getting up very early and was seldom in bed before midnight. His daily round was never hurried and often interrupted by the innumerable acts of personal kindness which will be long remembered by his friends and patients".

Dr. J. C. BROOM

C. R. R., one of Dr. Broom's younger friends, who had already corresponded with him from Malaya for three years, writes of their first meeting in 1956:

"I remember a slightly diminutive, very kindly, elderly man with a grey toothbrush moustache and sparkling rather boyish eyes. I was impressed by his scholarly air and intense interest in his work; he was never too busy to discuss some aspect or to explain a problem. I was given access to all his reference files, and through him accorded many privileges throughout the Wellcome Institute. He set an example in his industriousness and passionate dedication to honesty and endeavour. He considered science as a high cultural value, and this was evident in his delightfully lucid style of writing, and interest in the historical aspects of medicine. He felt strongly the responsibility of the older to the younger person, and his advice on personal problems was straightforward and honest. His friendly encouragement and sympathetic understanding has since sustained me several times, and I will miss seeing him when I visit England."

Notes and News

A DISPOSABLE FACE MASK

To prevent droplet infection, a new disposable mask has been evolved which, we are informed, prevents bacteria-laden particles from passing sideways as well as forwards from the wearer's mouth. Embodying an impervious layer of paper, this mask has been tested at the Children's Hospital, Birmingham, and Dr. K. B. Rogers, clinical pathologist to the hospital, has given us some particulars.

After the masks had been worn for over an hour, tests were made at quarter-hour intervals, as follows:

A petri dish containing 10% blood-agar medium was held about 12 in. in front of the wearer's mouth and "tut" was spoken ten times, in a normal but slightly raised voice. A second blood-agar plate was held in the same position while a single explosive "spraying spit" [1] was emitted.

None of the plates exposed during these experiments grew any organisms. "Though this result was no better than that obtained with the standard cotton mask used in this hospital which has a sheet of 'Cellophane' inserted between two layers of cotton fabric, further testing showed that the disposable masks had certain advantages. The cotton-fabric masks are square and they tend to leave a slight gap on either side of the wearer's nose where the nose protrudes from the face. The disposable mask is shaped to fit snugly round the nose. Plates held at right-angles to the wearer's mouth grew no organisms when the disposable mask was worn, but always grew organisms when the standard hospital mask was in place."

The disposable mask [2] is easily put in position and can be kept there with a cotton-covered strip of elastic which is sealed into the free edges of the mask and is so arranged that two loops of thin elastic can be placed round the wearer's ears.

When the masks were autoclaved in the hospital's theatre autoclave at 20 lb. pressure (126°C) the texture of the elastic was slightly altered, so that it was liable to stretch when pulled out to place it round the ears. But this did not happen when they were autoclaved at 10 or 15 lb. pressure (155° and 121°C).

These masks were unsuitable for anyone who had a cold with profuse nasal discharge, for the paper becomes sodden and liable to tear. But, as Dr. Rogers says, "it is not suggested that people with heavy colds should be on duty".

COOPERATIVE GERIATRICS

LAST year the National Corporation for the Care of Old People announced that they were going to compile a register of social and medical research on the welfare of old people. This year [3] they are able to announce that a master copy of the register is now in existence and can be consulted at their offices. It includes projects that are being made by universities, hospitals, local authorities, voluntary organisations, and individuals. It is hoped that printed copies will be ready for distribution in the next few months. Though the register may not be absolutely complete, it is a substantial and useful start which, the corporation points out, shows "not only what is being done but what is not".

College of General Practitioners

Upjohn travelling fellowships—Applications are invited from members of this college for not less than 15 fellowships of up to £200 each in value.

These fellowships are to enable general practitioners to spend a minimum of two weeks' postgraduate study at their old teaching hospitals or at any other hospitals, clinics, health centres, or general practices in the United Kingdom or Eire. They are not available for study overseas. Further information may be had from the secretary of the college, 41, Cadogan Gardens, London, S.W.3. The closing date for applications is Aug. 1.

1. Studies in Air Hygiene. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 262, plate 12. 1948.
2. This mask is being marketed by Smith & Nephew—Southalls Ltd., 256, Old Street, London, E.C.1, and will be called 'S. and N. Disposable Promask'.
3. Twelfth annual report of the corporation. (Nuffield Lodge, Regent's Park, London, N.W.1.)

University of Durham

Dr. R. J. Scothorne, senior lecturer in anatomy in the University of Glasgow, has been appointed to the chair of anatomy at King's College.

Dr. Scothorne, who is 39 years of age, was educated at the Royal Grammar School, Newcastle upon Tyne, and Leeds University. He graduated B.SC. with honours in anatomy in 1941 and continued his studies at the University of Chicago with a Rockefeller studentship. He graduated M.D. Chicago in 1943, and on his return to this country the following year he took the degree of M.B. Leeds with honours. He was lecturer in anatomy at Leeds from 1945 to 1950 when he took up his present post at Glasgow. In 1951 he took the degree of M.D. with distinction, and in 1955 he was awarded the Struthers gold medal. His published work includes papers on the comparative embryology of the thyroid gland and the thymus, on tissue transplantation immunity, and on salt and water balance in birds.

National University of Ireland

Dr. O. T. D. Loughnan has been appointed lecturer in therapeutics at University College, Cork.

The degree of M.D. has been conferred on J. M. Lavelle.

Royal College of Surgeons of England

At a meeting of the council on April 14, with Sir James Paterson Ross, the president, in the chair, Prof. G. V. R. Born was admitted as Vandervell professor of pharmacology.

The following, as medical practitioners of twenty years' standing, were elected fellows of the college without examination:

Dr. Frankis Evans, Surgeon Capt. J. L. S. Coulter, Dr. E. F. Scowen, Dr. T. J. Warren (Brazil), Prof. E. C. Amoroso, Prof. Jannie Louw (Cape Town).

The Jacksonian prize for 1959 was awarded to Mr. G. Slaney. Dr. B. Orban of Chicago was appointed Webb-Johnson lecturer for 1958–61, and Mr. R. G. Smith, Laming Evans senior research fellow in orthopædics.

The following were elected fellows in the Faculty of Anæsthetists without examination.

J. Boreau (France), W. G. Cullen (Canada), J. U. Forbes (Kuwait), R. Frey (Germany), M. Prasad (India).

Jephcott Lecture

This lecture will be given by Sir Howard Florey on Monday, May 9, at 7 P.M., at 1, Wimpole Street, London, W.1. His subject will be coronary-artery disease. Tickets may be had from the secretary of the Jephcott Lecture Trust, 1, Carlos Place, W.1.

Central Midwives Board

Mr. Arnold Walker has been re-elected chairman and Prof. A. A. Moncrieff deputy chairman of the board.

British Council for Rehabilitation

The annual general meeting of this Council will be held on Thursday, May 12, at 3 P.M., in H.Q.S. Wellington, Temple Stairs, Victoria Embankment, London, W.C.2. Sir Harry Platt will give the Dame Georgiana Buller lecture. He will speak on pioneers of rehabilitation.

Committee on Noise

The 12 members of the committee which the Government has set up to consider noise and its effects will include Dr. T. Ferguson Rodger, professor of psychological medicine in Glasgow University, who will act as deputy chairman, and Dr. R. C. M. Pearson, medical officer of health for Newcastle upon Tyne.

Provision of Animals for Cancer Research

A symposium on this subject will be held at 1, Wimpole Street, London, W.1, on Monday, May 23, at 9.30 A.M., with Prof. J. S. Mitchell in the chair.

The speakers will include Prof. Alexander Haddow, Dr. P. R. Peacock, Dr. D. L. Woodhouse, Prof. F. Bergel, Dr. P. Loustalot (Basle), Dr. M. H. Salaman, Dr. K. E. K. Rowson, Dr. George E. Jay, Jr. (Bethesda), Dr. J. G. Bennette, Dr. June East, Dr. J. G. Carr, Dr. F. Kingsley Sanders, and Mr. J. D. Whittaker. Further information may be had from the director, Laboratory Animals Centre, M.R.C. Laboratories, Woodmansterne Road, Carshalton, Surrey.

International Conference on Congenital Malformations

This conference will be held in London from July 18 to 22 (see *Lancet*, Feb. 13, 1960, p. 375). Registration forms may be had from the secretariat of the conference, 67, New Bond Street, Dering Yard, London, W.1, and should be returned not later than May 1.

The International Society for Clinical and Experimental Hypnosis

Prof. Alexander Kennedy has been elected the first president of the British national division of this society; Mr. Eric E. Wookey, chairman of council; Dr. Michael Fenton, hon. treasurer; and Dr. A. A. Mason (24, Avenue Road, Regent's Park, London, N.W.8), hon. secretary.

Medical Association for the Prevention of War

On Saturday, May 28, at 2.30 P.M., at 45, Russell Square, London, W.C.1, this Association will hold a symposium on the present-day significance of medical science in relation to war prevention. The speakers will include Dr. Anthony Storr and Dr. Jeffrey Boss. The hon. secretary of the association is Dr. Dorothy Arning, 127, King Henry's Road, N.W.3.

Colour Television Demonstrations

Demonstrations, arranged by the Kensington and Hammersmith division of the British Medical Association and the West London faculty of the College of General Practitioners, will be transmitted from the Postgraduate Medical School of London and the Hammersmith Hospital to an audience at the Royal College of Surgeons of England, Lincoln's Inn Fields, W.C.2, at 8.30 P.M. from Monday to Thursday, May 16 to 19. The subjects chosen for demonstrations are repair of hiatus hernia, pituitary ablation, heart surgery, and dermatology. Further particulars may be had from the secretary of the B.M.A., B.M.A. House, Tavistock Square, W.C.1.

A few scholarships (in the form of free accommodation and board) are offered to medical students who wish to attend the international summer course to be held from July 15 to 30 at the Institute of Hydrology and Climatology of the University of Clermont-Ferrand. Applications should be sent to the director of the institute, Boulevard Gergovia, Clermont-Ferrand, France.

The annual general meeting of the Kent Pædiatric and Child Health Society will be held on Saturday, May 7, at 3 P.M., at Maidstone Technical School for Girls, Albion Place, Maidstone. Dr. A. D. B. Clarke will speak on uses and abuses of the I.Q. test.

A semipermanent exhibition, arranged by Dr. E. J. Moynahan, on pædiatric dermatology will be held at the Institute of Dermatology, Lisle Street, W.C.2, from May 2 to 25.

The London Medical Orchestra is giving a concert on Saturday, April 30, at 8 P.M. at the Royal College of Surgeons, Lincoln's Inn Fields, W.C.2, in aid of the Imperial Cancer Research Fund.

Appointments

BINNS, T. P., M.R.C.S., D.P.H.: school M.O., North Riding of Yorkshire.
CAMPBELL, F. N., M.B. Edin.: school M.O., Birmingham.
EVANS, MYRDDIN, M.B., B.SC. Wales, M.R.C.P., D.P.M.: consultant psychiatrist, Whitchurch Hospital, near Cardiff.
GAMPEL, BASIL, M.B. Cape Town: house-surgeon, orthopædic and plastic departments, The Hospital for Sick Children, Great Ormond Street, London.
GREEN, M. R., M.B. Birm.: school M.O., Birmingham.
GRIMSHAW, V. A., M.B. Cantab., F.F.A. R.C.S.: consultant anæsthetist, United Leeds Hospitals.
MACLEOD, M. C., M.D. Glasg., D.P.H.: deputy county and deputy principal school M.O., Worcestershire.
MARSHALL, B. A., M.B. St. And., D.O.M.S.: consultant ophthalmologist, Doncaster group of hospitals.
ROBERTSON, MOIRA C., B.M. Oxon.: assistant M.O. (maternity and child welfare), Leeds.
TEMPANY, EDWARD, M.B. N.U.I., M.R.C.P.I., D.C.H.: house-physician, The Hospital for Sick Children, Great Ormond Street, London.
WINSTANLEY, JOHN, M.C., M.B. Lond., F.R.C.S.: part-time ophthalmic surgeon, St. Thomas's Hospital, London.

Liverpool Regional Hospital Board:

BROWNE, JAMES, M.D. Belf., D.P.M.: consultant psychiatrist and deputy medical superintendent, Deva Hospital.
MACCARTHY, D. F., M.CH. N.U.I.: senior casualty officer, Chester and district H.M.C.
ROGERSON, MILLICENT M., M.B. Lond., D.C.H.: senior M.O. (S.H.M.O.), Olive Mount Children's Hospital.

Diary of the Week

APRIL 24 TO 30

Monday, 25th

HUNTERIAN SOCIETY
8.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Sir Albert Richardson: Dr. Johnson's England with Special Reference to London.
INSTITUTE OF ACCIDENT SURGERY
5.30 P.M. (Department of Anatomy, University of Birmingham.) Lieut.-General Sir Alexander Drummond: Care of the Injured. (Ruscoe Clarke lecture.)

Tuesday, 26th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Sir Russell Brain, Dr. A. T. Richardson, Dr. Samuel Nevin: The Acquired Myopathies.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Prof. J. H. McK. Pinkerton: Antenatal Pædiatrics in the First Trimester.
ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) *Medical Section.* Dr. E. G. Knox: Susceptibility to Acute Respiratory Diseases in Children.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Dr. F. D. Johnston (Michigan): Acoustics of Stethoscope Design.

Wednesday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. A. A. Barton: Wings. (Arnott demonstration.)
UNIVERSITY OF LONDON
5.15 P.M. (London Hospital Medical College, Turner Street, E.1.) Prof. John Romano (New York): Teaching of Psychiatry to Medical Students.
ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology.* Prof. P. A. Bastenie (Brussels): Studies on Endemic Cretins in the Belgian Congo. Prof. Douglas Hubble: Management of the Adrenogenital Syndrome in Childhood. Dr. Roger Williams: Adrenocortical Tumour, Hypoglycæmia, and Excessive Secretion of Compound S.
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
2 P.M. Prof. G. J. Cunningham: Cellular Damage.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Lymphocytic Infiltration of the Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. Vernon Thompson: Constrictive Pericarditis.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Dr. Hans Popper (New York), Dr. Leon Schiff (Cincinnati): Liver Disease.
UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary.) Mr. Wylie McKissock: Surgical Treatment of Intracerebral Hæmorrhage. (Litchfield lecture.)

Thursday, 28th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. W. J. Metcalfe: Arterial Embolism in the Lower Limbs. (Hunterian lecture.)
ROYAL SOCIETY OF MEDICINE
8 P.M. *Urology.* Mr. J. C. Anderson: Treatment of Bladder Tumours.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Richard Schatzki: Aspects of Dysphagia.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. R. M. Harman: Anatomy of Skin—Benign Skin Conditions with Reference to Radiotherapy.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5 P.M. Dr. Eliot Slater: Epileptic Psychosis.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Mr. David Levi: Acute Abdomen.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthetics.* Dr. G. N. Mulliner: Anæsthesia and Body Temperature. Dr. J. C. Richardson: New Developments in Anæsthesia for Cardiac Surgery.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Dr. J. A. Simpson: Myasthenia Gravis.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. C. L. Oakley: Sites of Antibody Production.

Friday, 29th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Prof. H. W. Rodgers: Diffuse Lesions of the Oral Mucosa.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Dr. C. H. Edwards: Headache and Facial Pain.
5.30 P.M. Mr. Anthony Radcliffe: Surgery or Radiotherapy for Cancer of the Neck.
BRITISH ASSOCIATION OF PHYSICAL MEDICINE
10.15 A.M. (King's College Hospital, Denmark Hill, S.E.5.) Opening of two-day meeting.

Saturday, 30th

FACULTY OF RADIOLOGISTS
9.45 A.M. (Manchester Royal Infirmary.) Opening of one-day provincial meeting.

CORRIGENDUM: *Speed of Action of Aspirin, Soluble Aspirin, and Buffered Aspirin.*—In Dr. Peter Sleight's article of Feb. 6 (p. 305), the constitution of 'Bufferin' was incorrectly stated. This product consists of acetylsalicylic acid plus aluminium dihydroxy aminoacetate plus magnesium carbonate.